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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GERTZ, Barry, J. [US/US]; 44 Fairview Avenue, Summit, NJ 07901 (US). RODAN, Gideon, A. [US/US]; 827 Deerfield Lane, Bryn Mawr, PA 19010 (US). SMITH, Roy, G. [GB/US]; 122 East Dudley Avenue, Westfield, NJ 07090 (US). WYVRATT, Matthew, J. [US/US]; 1612 Grouse Lane, Mountainside, NJ 07092 (US). PATCHETT, Arthur, A. [US/US]; 1090 Minisink Way, Westfield, NJ 08090 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: COMBINATION OF BISPHOSPHONATES AND GROWTH HORMONE SECRETAGOGUES

(57) Abstract

Bisphosphonates in combination with growth hormone secretagogues reduce the deleterious effects of osteoporosis in elderly patients.

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TITLE OF THE INVENTION
COMBINATION OF BISPHOSPHONATES AND GROWTH HORMONE SECRETAGOGUES

BACKGROUND OF THE INVENTION

Bisphosphonates (bisphosphonic acids) are known to inhibit bone resorption and are useful for the treatment of bone lithiasis as disclosed in U.S. Patent 4,621,077 to Rosini, et al. The treatment of osteoporosis with calcitonin, alone and in combination with human growth hormone was examined by Aloia, et al., Metabolism, 34(2) 124-129 (1985). This publication ascribes no benefit in the treatment of osteoporosis from combining calcitonin therapy with the administration of growth hormone. The effects of growth hormone itself in the treatment of osteoporosis was studied by Aloia, et al., J. Clin. Endocrinol. Metab., 54, 992-999 (1976). Certain non-peptidal growth hormone secretagogues are known to stimulate the pituitary gland to increase its secretion of growth hormone with utility in growth hormone deficient children and adults, in severe burn victims, in the treatment of Turners syndrome, for reversing the adverse effects of glucocorticoid treatment, for treating muscle and excercise tolerance deficiencies in growth hormone deficient adults, and for the treatment of osteoporosis. Compounds with growth hormone secretagogue activity are disclosed in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/13696; and Science, 260, 1640-1643 (June 11, 1993). Additional compounds with growth hormone secretagogue activity are described herein.

The literature discloses a variety of bisphosphonic acids which are useful in the treatment and prevention of diseases involving bone resorption. Representative examples may be found in the following: U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S.

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Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,007; U.S. Patent No. 4,942,157; U.S. Patent No. 5,227,506; EPO Patent Pub. No. 0,252,504; and J. Org. Chem., 36, 3843 (1971).

The preparation of bisphosphonic acids and halo-bisphosphonic acids is well known in the art. Representative examples may be found in the above mentioned references which disclose the compounds as being useful for the treatment of disturbances of calcium or phosphate metabolism, in particular, as inhibitors of bone resorption.

SUMMARY OF THE INVENTION

This invention is concerned with the combination of a bisphosphonate (bisphosphonic acid) and a growth hormone secretagogue for the treatment and the prevention of disturbances of calcium and phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially, osteoporosis, Paget's disease, malignant hypercalcemia, and metastatic bone disease. This particular combination produces unexpected results in the treatment and the prevention of such clinical disturbances. Thus, it is an object of the instant invention to describe the combination of the two drugs in the treatment and prevention of diseases involving bone resorption, especially, osteoporosis. In addition, it is an object of the instant invention to describe the preferred compounds from each type of compounds which are used in the instant combination. It is a still further object of this invention to describe compositions containing each of the compounds for use in the treatment of osteoporosis. Further objects will become apparent from a reading of the following description.

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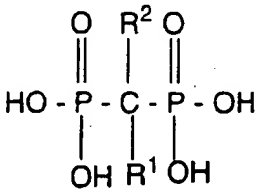
DESCRIPTION OF THE INVENTION

The instant combination for the treatment and prevention of diseases involving bone resorption, especially osteoporosis in elderly patients, contains as a first element which is a bisphosphonate compound, especially a compound selected from the group of bisphosphonates (bisphosphonic acids) described by the following structural formula:



X

wherein:

R^1 is selected from the group consisting of:

(a) C_{1-5} alkyl, unsubstituted or substituted with:
  (1) NH_2,
  (2) pyridyl,
  (3) pyrrolidyl,
  (4) NR^3R^4
(b) NR^5,
(c) SR^6, and
(d) Cl;

R^2 is H, OH, or Cl;

R^3 is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-10} alkyl; and

R^6 is aryl;

or a pharmaceutically acceptable salt thereof.

The above Formula X also includes the salts of such compounds formed with alkali metals, organic bases and basic amino acids.

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The preferred compounds of the above Formula X are described where R^1 is C_1-C_5 alkyl substituted with amino or pyridyl, most preferably at the terminal carbon, and R^2 is hydroxy. The preferred salts are formed with alkali metals, most preferably sodium.

The most preferred bisphosphonates are selected from the group of the following compounds: alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid;
or any pharmaceutically acceptable salt thereof.

The production of bisphosphonic acids is well known in the literature. Representative examples may be found in the following: U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,578,376; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,761,406; U.S. Patent No. 4,922,007; U.S. Patent No. 4,942,157; U.S. Patent No. 5,227,506; EPO Patent Pub. No. 0,252,504; and J. Org. Chem., 36, 3843 (1971).

In the instant combination for the treatment of osteoporosis, the second element is composed of a growth hormone secretagogue.

Representative growth hormone secretagogues are disclosed in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/13696; and *Science, 260*, 1640-1643 (June 11, 1993).

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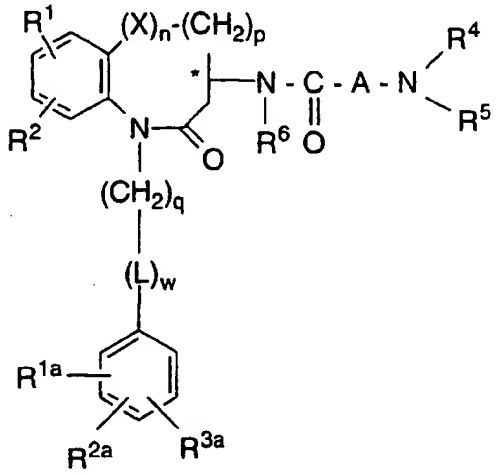
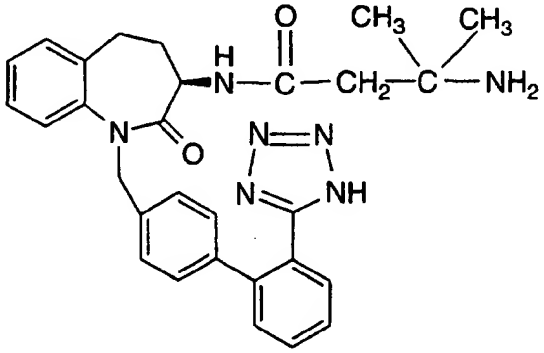
A generic formula for the growth hormone secretagogues set forth in U.S. Patent No. 5,206,235 is as follows:



wherein the various substituents are as defined in U.S. Patent 5,206,235.

The most preferred benzolactam compounds therein are identified as having the following structures:



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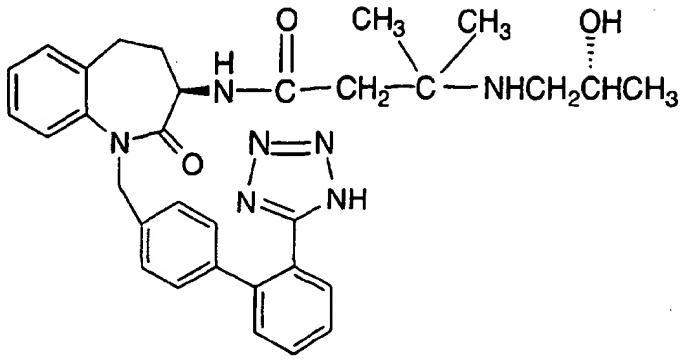
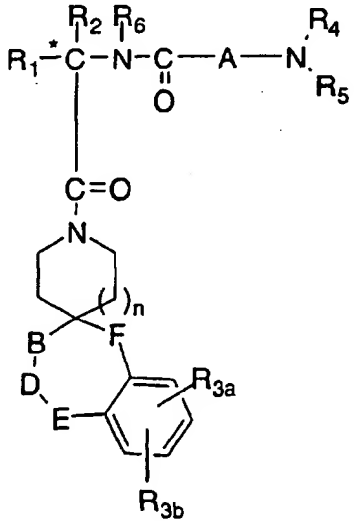
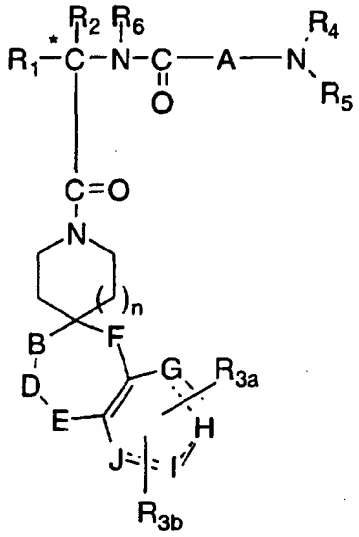


Additional representative growth hormone secretagoues are disclosed in PCT Patent Pub. No. WO 94/13696 as spiro compounds of the following structural Formulas I and II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl,

-aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

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wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, $OC(O)$, $C(O)O$, or $-CR_2=CR_2-$, or $-C\equiv C-$,
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, $-OR_2$, cyano, $-OCF_3$, methylenedioxy, nitro, $-S(O)_mR$, $-CF_3$ or $-C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $-S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form $-(CH_2)_rL_a(CH_2)_s-$ where L_a is $-C(R_2)_2-$, $-O-$, $-S(O)_m-$, or $-N(R_2)-$, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

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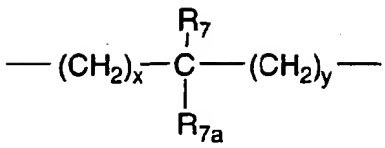
A is:



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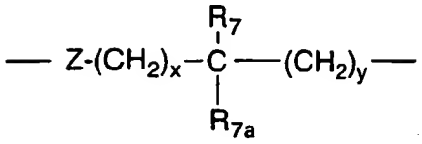

wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=0, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -$N=CR_{10}$- or -$CR_{10}=N$-, or B and D, or D and E taken together may be -$CR_8=CR_{10}$-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

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R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2 (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m R_{2a}$, -C(O)NHSO_2(CH_2)$_q$-aryl, -SO_2NHC≡N, -SO_2NHC(O)R_{2a}, -SO_2NHC(O)(CH_2)$_q$aryl, -N(R_2)C(O)N(R_{2a})(R_{2a}), -N(R_{2a})C(O)N(R_{2a})(CH_2)$_q$-aryl, -N(R_{2a})(R_{2a}), -N(R_{2a})C(O)R_{2a}, -N(R_{2a})C(O)(CH_2)q aryl, -OC(O)N(R_{2a})(R_{2a}), -OC(O)N(R_{2a})(CH_2)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

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In the above structural formulas and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propenyl, butenyl, butadienyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propinyloxy, isobutenyloxy, 2-hexenyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" is intended to include phenyl and naphthyl and aromatic residues of 5- and 6- membered rings with 1 to 3 heteroatoms or fused 5 or 6 membered bicyclic rings with 1 to 3 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, furan, pyrimidine, and thiadiazole.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Most preferred growth hormone secretagogues employed in the combination of the instant invention are realized in structural Formula V:

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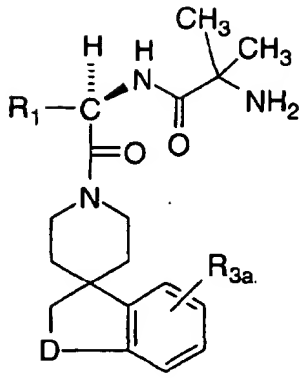
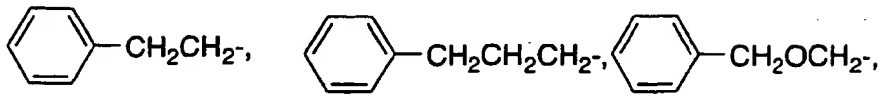
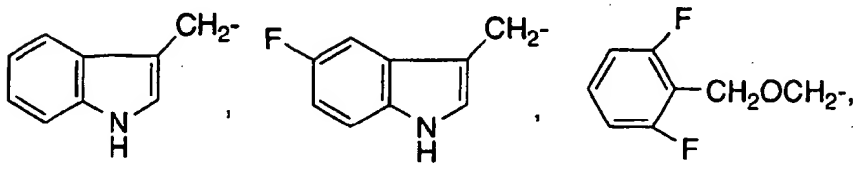
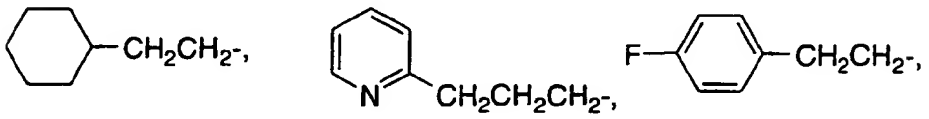


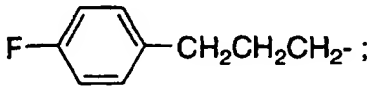
V

wherein R1 is selected from the group consisting of:









R3a is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)m-, N(R2), NSO2(R2), NSO2(CH2)taryl, NC(O)(R2), NSO2(CH2)qOH, NSO2(CH2)qCOOR2, NSO2(CH2)qC(O)-N(R2)(R2), N-SO2(CH2)qC(O)-N(R2)(CH2)wOH,

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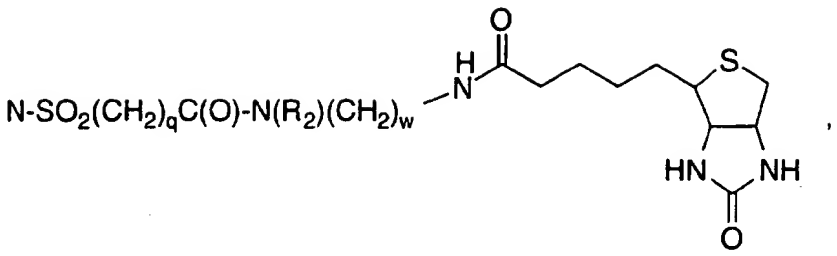

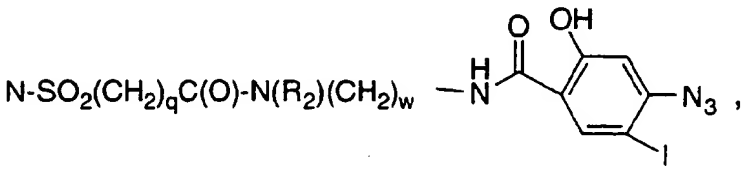

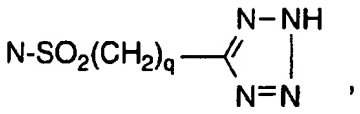

and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Representative most preferred growth hormone secretagoues employed in the present combination include the following:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)e:. yl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

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11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

Expecially preferred growth hormone secretagogues include:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

and pharmaceutically acceptable salts thereof.

The production of bisphosphonic acids is well known in the literature. Representative examples of various bisphosphonic acid compounds and methods for the preparation may be found in the following: U.S. Patent No. 3,251,907; U.S. Patent No. 3,422,137; U.S. Patent No. 3,584,125; U.S. Patent No. 3,940,436; U.S. Patent No. 3,944,599; U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,621,077; U.S. Patent No. 4,746,654; U.S. Patent No. 4,624,947; U.S. Patent No. 4,922,007; EPO Patent Pub. No. 0,252,504; and J. Org. Chem., 36, 3843 (1971).

Full descriptions of the preparation of the growth hormone secretagoues is found in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/13696; and Science, 260, 1640-1643 (June 11, 1993).

The preparation of growth hormone secretagogues of Formulas I and II employed in the combinations of the present invention can be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I and II in a sequential manner are presented in the following reaction schemes.

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The protected amino acid derivatives **1** are, in many cases, commercially available where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives **1** can be prepared by literature methods. Many of the spiro piperidines and spiroazepines (n=2) of Formula **2** and **2a** are known in the literature and can be derivatized on the phenyl or heteroaryl by standard means, such as halogenation, nitration, sulfonylation, etc. Alternatively, various phenyl or heteroaryl substituted spiro piperidines and spiroazepines (n=2) can be prepared following literature methods using derivatized phenyl and heteraryl intermediates. In Schemes subsequent to Scheme I, the synthetic methods are illustrated only with spiropiperidines although it will be appreciated by those skilled in the art that the illustrated transformations can also be carried out in the higher homolog series to afford compounds of Formulas **I** and **II** with n=2.

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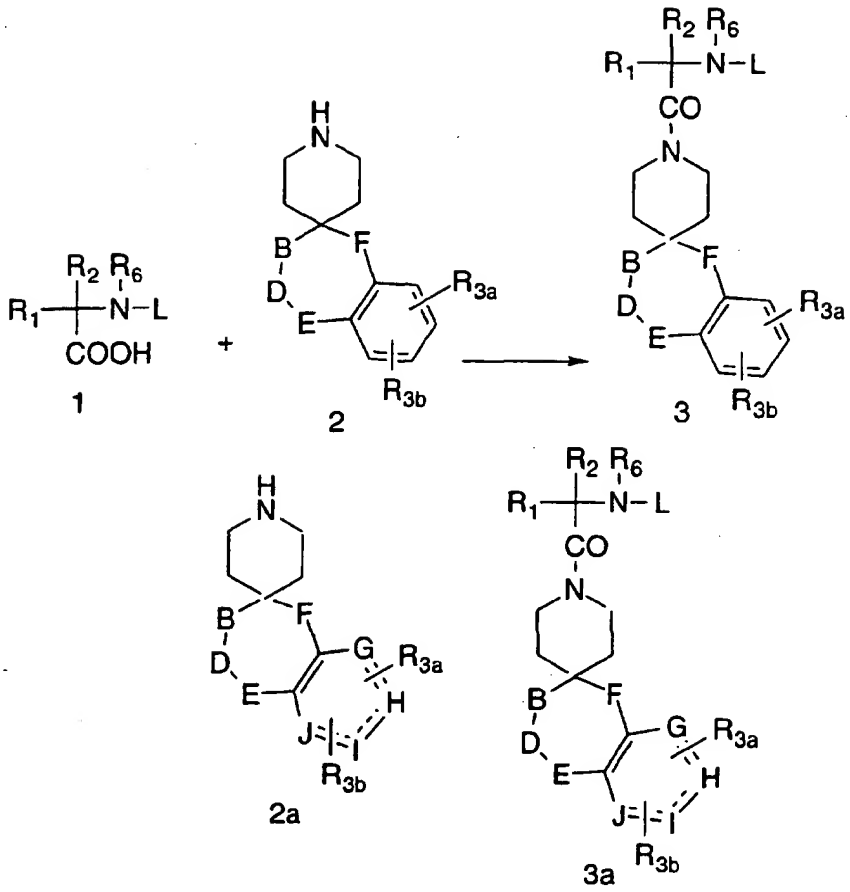
SCHEME 1



Intermediates of Formulas **3** and **3a** can be synthesized as described in Scheme 1. Coupling of spiro piperidines of Formula **2** and **2a** to protected amino acids of Formula **1**, wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as DCC or EDC in the presence of HOBT. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane. Separation of unwanted side products, and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978)), MPLC or preparative TLC.

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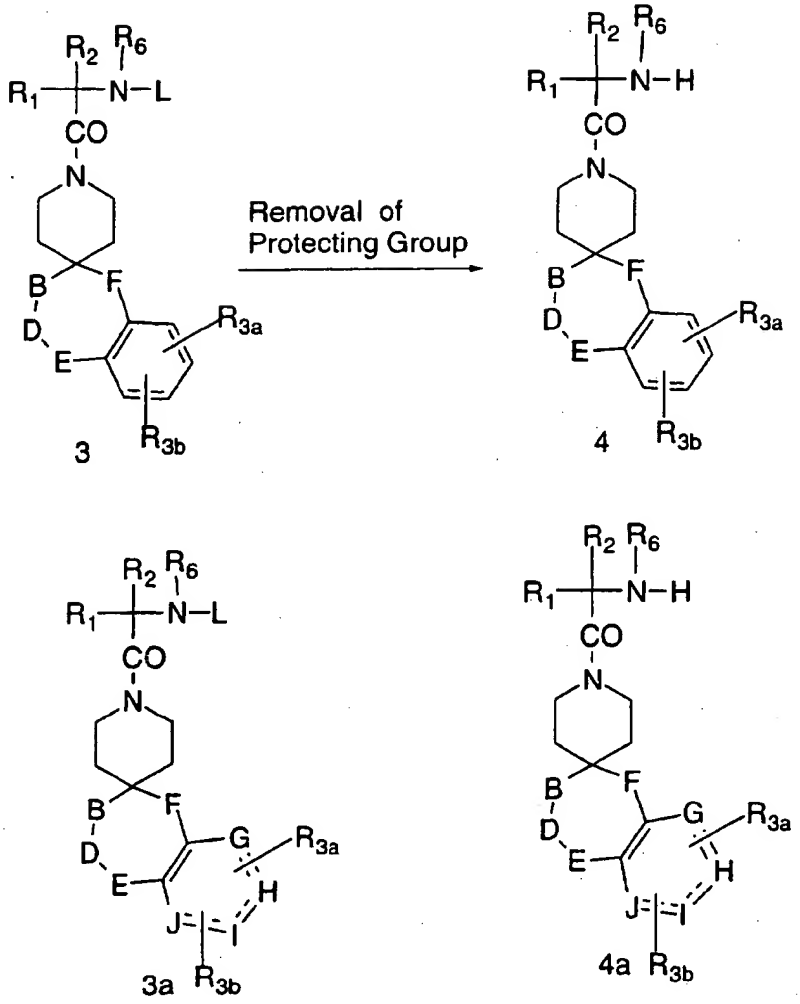
SCHEME 2



Conversion of **3** and **3a** to intermediates **4** and **4a** can be carried out as illustrated in Scheme 2. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of palladium or platinum catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxy carbonyl groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Removal of BOC protecting groups is

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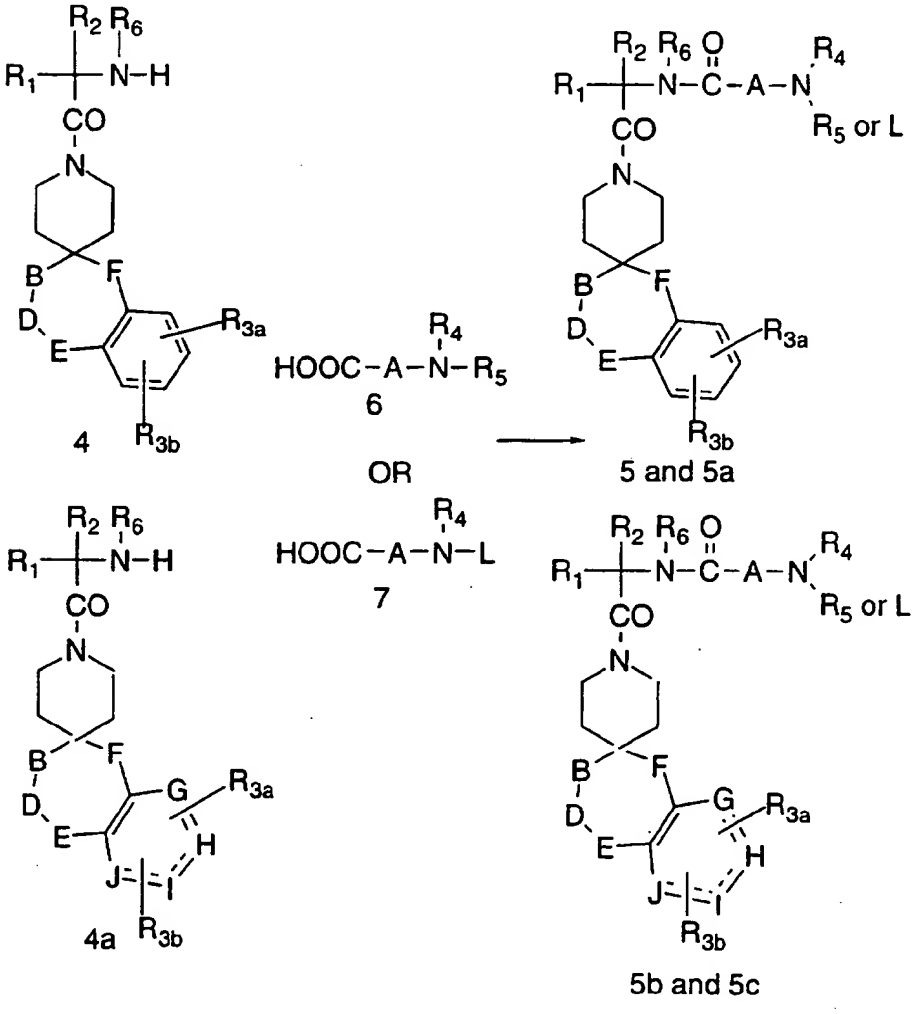
carried out in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Greene, T; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991.

SCHEME 3



Intermediates of Formula **5** and **5b**, wherein A is a methylene or a substituted methylene group, can be prepared as shown in Scheme 3 by coupling of intermediates of Formula **4** and **4a** to amino acids of Formula **6**, once again, in an inert solvent such as dichloro-

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methane by a coupling reagent such as EDC or DCC in the presence of HOBT. These amino acids 6 are known amino acids or amino acids readily synthesized by methods known to those skilled in the art. Alternatively, the coupling can also be effected with a coupling reagent such as BOP in an inert solvent such as dichloromethane. Also if R_4 or R_5 is a hydrogen then amino acids of Formula **7** are employed in the coupling reaction, wherein L is a protecting group as defined above, to give **5a** and **5c**. Deprotection of **5a** and **5c** (L = protecting group) can be carried out under conditions known in the art.

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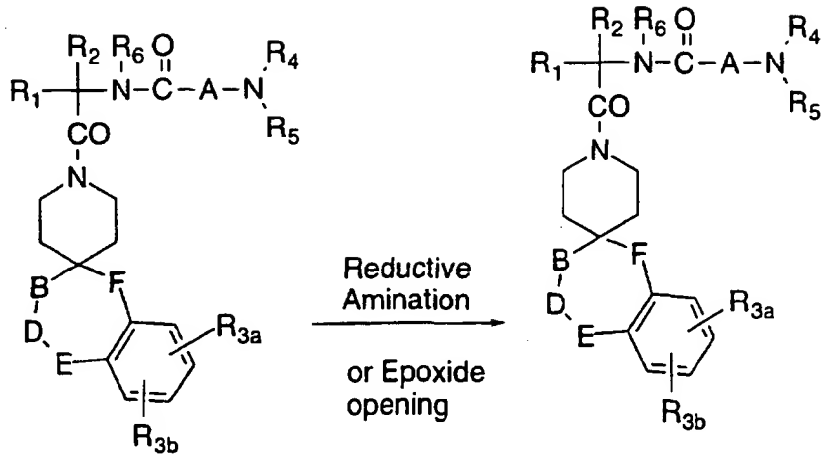
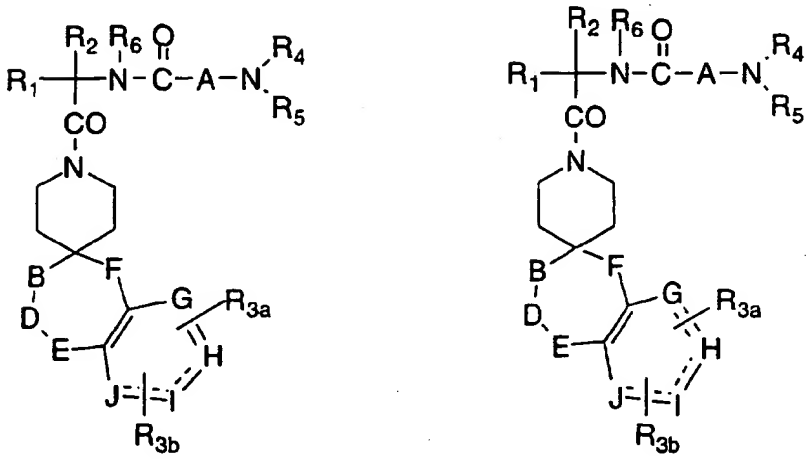
SCHEME 4



I R_4 and/or R_5 = H

I where R_4 and/or R_5 is C1-C6 alkyl or substituted alkyl



II R_4 and/or R_5 = H

II where R_4 and/or R_5 is C1-C6 alkyl or substituted alkyl

Compounds of Formula I and II wherein R4 and/or R5 is a hydrogen can be further elaborated to new Compounds I and II (preferred side chain R7 = CH_2-CH(OH)-CH_2X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive amination of I and II with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel

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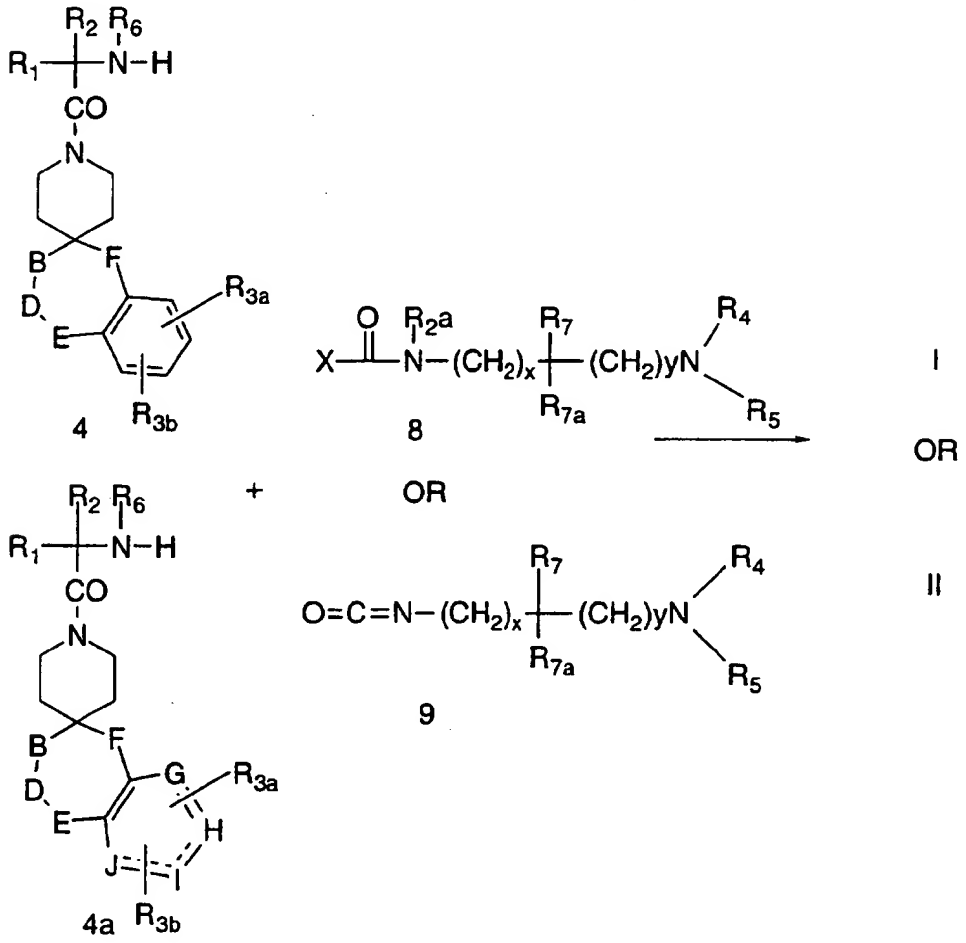
catalysts or with chemical reducing agents such as sodium cyanoborohydride in an inert solvent such as methanol or ethanol. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

SCHEME 5



Compounds of Formula **I** and **II**, wherein A is $N(R_2)$-$(CH_2)_z$-$C(R_7)(R_{7a})$-$(CH_2)_y$, can be prepared as shown in Scheme 5 by reacting **4** or **4a** with reagents **8**, wherein X is a good leaving group such as Cl, Br, I, imidazole. Alternatively, **4** and **4a** can be reacted with an isocyanate of Formula **9** in an inert solvent such as 1,2-dichloroethane. If R4 or R5 is hydrogen in the final product, the

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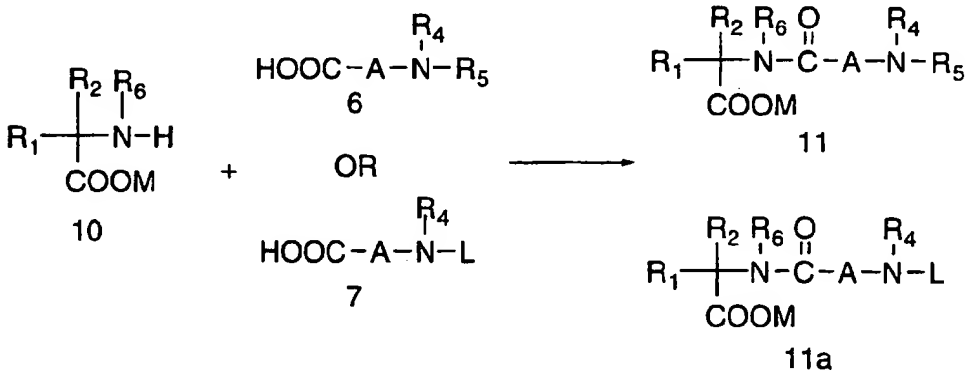
reagents 8 and 9 will bear a removable protecting group L in place of R4 or R5.

The Compounds I and **II** of the present invention can also be prepared in a convergent manner as described in reaction Schemes 6, 7 and 8.

The protected amino acid derivatives **10** are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of a protected amino acid with a diazoalkane and removal of a protecting group L, the reaction of an amino acid with an appropriate alcohol in the presence a strong acid like hydrochloric acid or p-toluenesulfonic acid. Synthetic routes for the preparation of new amino acids are described in Schemes 14, 15, and 16.

SCHEME 6



Intermediates of Formula **11** and **11a**, can be prepared as shown in Scheme 6 by coupling of amines **10** to amino acids **6** and/or **7**, wherein L is a protecting group, as described above in Scheme 3. When a urea linkage is present in **11** or **11a**, it can be introduced as illustrated in Scheme 5.

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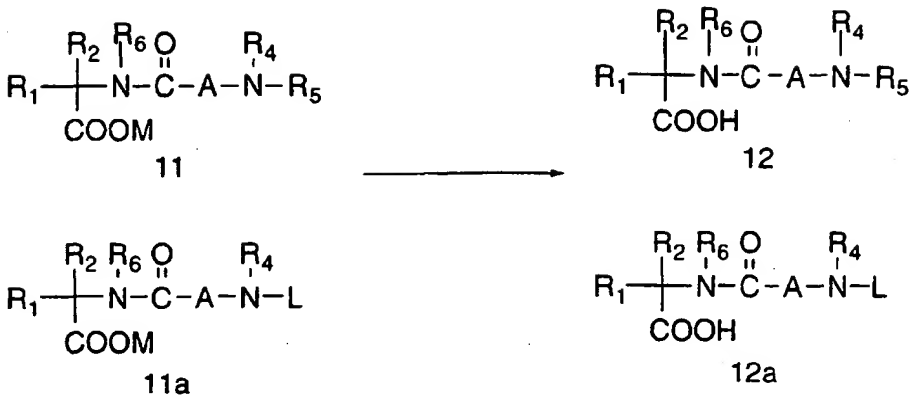
SCHEME 7



Conversion of the ester **11** or **11a** to intermediate acids **12** or **12a** can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see *J. Org. Chem.* **1982**, *42*, 587).

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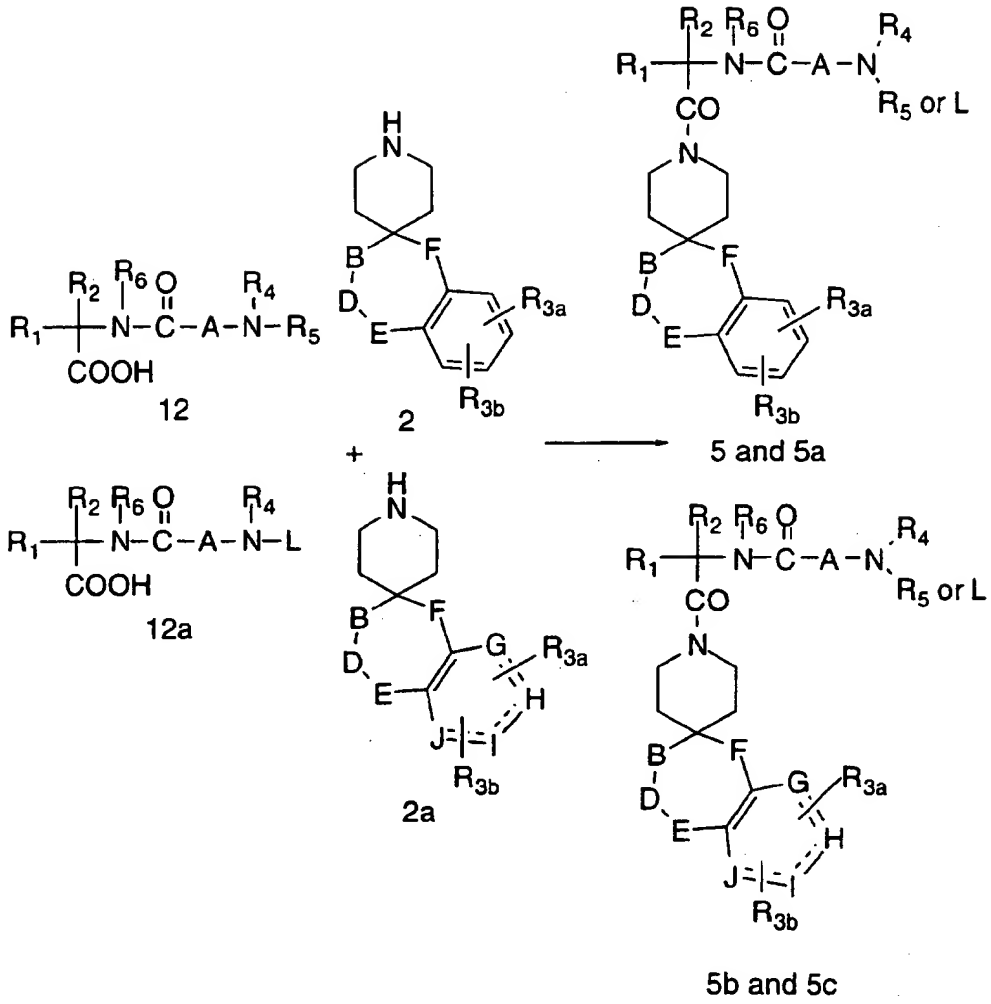
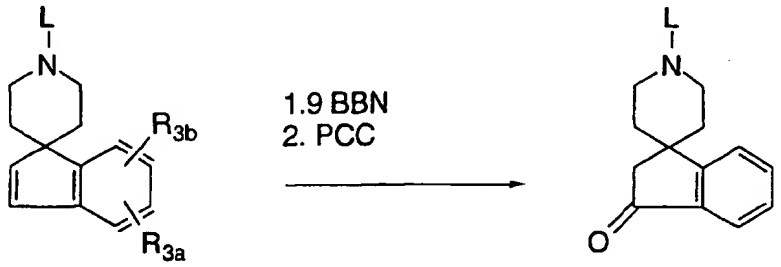
SCHEME 8



Acid **12** or **12a** can then be elaborated to **5** & **5a** and **5b** & **5c** as described in Scheme 8. Coupling of spiro piperidines of Formula **2** and **2a** to acids of Formula **12** or **12a**, wherein L is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane by a coupling reagent such as dicylohexyl carbodiimide (DCC) or EDC in the presence of 1-hydroxybenztriazole (HOBT). Alternatively, the coupling can also be effected with a coupling reagent such as benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate ("BOP") in an inert solvent such as dichloromethane. Transformation of **5a** & **5c** to **I** and **II** is achieved

by removal of the protecting group L. When R4 and/or R5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

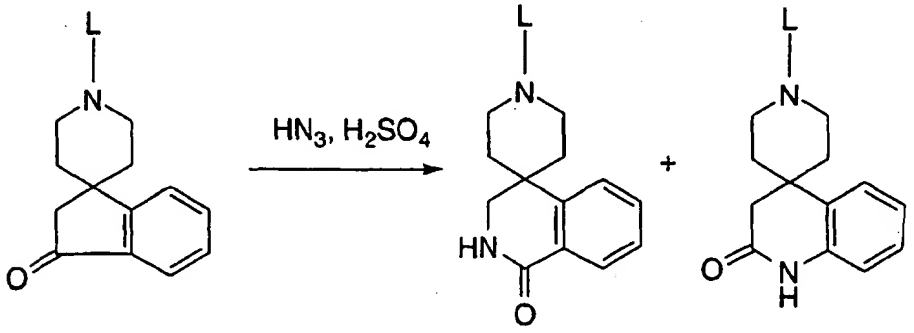
SCHEME 9



13 14

The preparation of oxygenated spiroindanyl piperidine intermediates is illustrated in Scheme 9 in which R_{3a} and R_{3b} are both hydrogens. Hydroboration of the protected spiroindene **13** followed by oxidative workup with pyridinium chlorochromate provides the spiroindanone **14**.

SCHEME 10



14 15 16

Conversion of spiroindanes into benzolactam intermediates is illustrated in Scheme 10. The treatment of the spiroindanone with hydrazoic acid in an inert solvent such as chloroform (Schmidt reaction) is one of the many suitable literature methods for this transformation.

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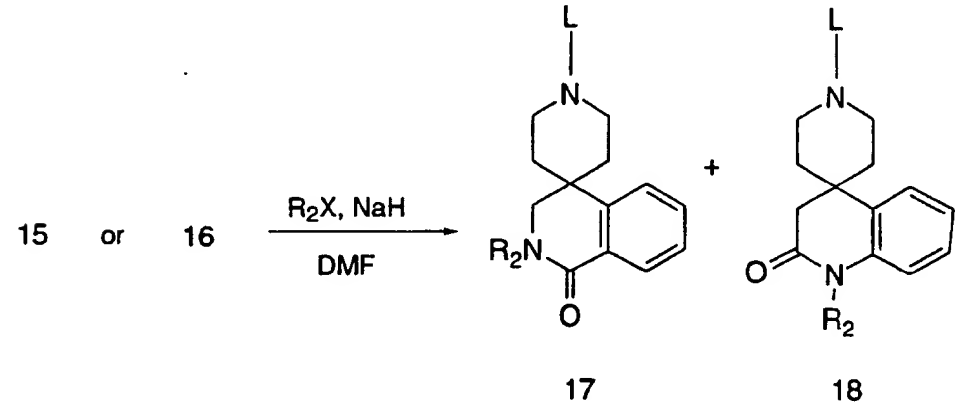
A mixture of two benzolactams is formed in this example. The isomers are easily separated by chromatography on silica gel. These intermediates can then be deprotected and incorporated into growth hormone secretagogues as depicted in Schemes 1 and 8 utilizing generic intermediate **2**.

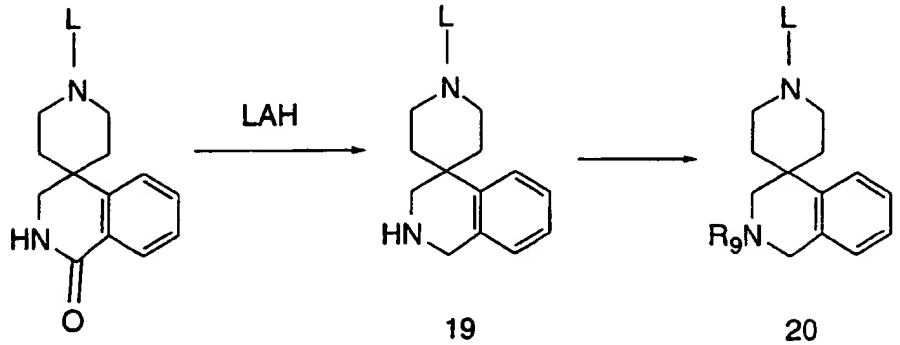
SCHEME 10A



17 18

Alkylation of **15** and **16** with an alkyl halide in a solvent such as DMF in the presence of NaH afford **17** and **18** (R_2 = C_1-C_4 alkyl).

SCHEME 11



15 19 20

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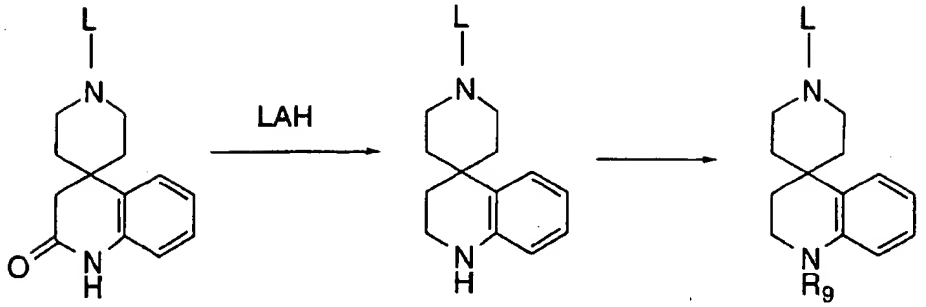
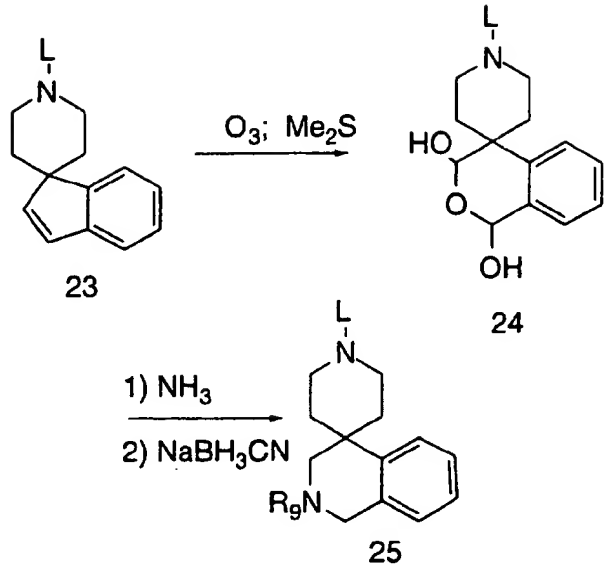
SCHEME 11A



16 21 22

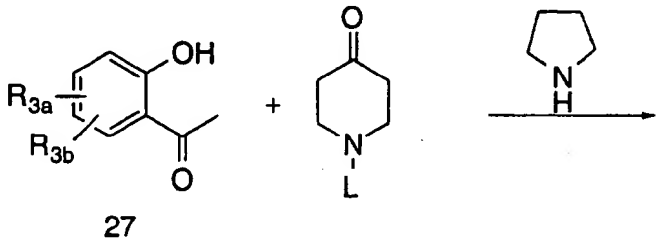
When L is an appropiate protecting group such as a benzyl group the amides can be reduced with lithium aluminum hydride to provide the amines **19** and **21**. These amines where R_2=H can then be alkylated, arylated, acylated, or reacted with substituted sulfonyl halides or isocyanates employing conditions known to those skilled in the art to afford Compounds **20** and **22**. Removal of the protecting group (L) by hydrogenolysis using a palladium catalyst provides intermediates that can be incorporated into the secretagogues of this invention using the chemistry illustrated in Schemes 1 and 8 shown above which utilize generic intermediate **2**.

SCHEME 12



Alternatively, the 1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidine] ring system can be prepared as outlined in Scheme 12. The ozonolysis of the protected spiroindene followed by dimethyl sulfide treatment gives a hemiacetal intermediate 24 which under reductive amination and acylation conditions provides amine 25. The amino protecting group (L) has been defined above.

SCHEME 13



SCHEME 13 (CONT'D)

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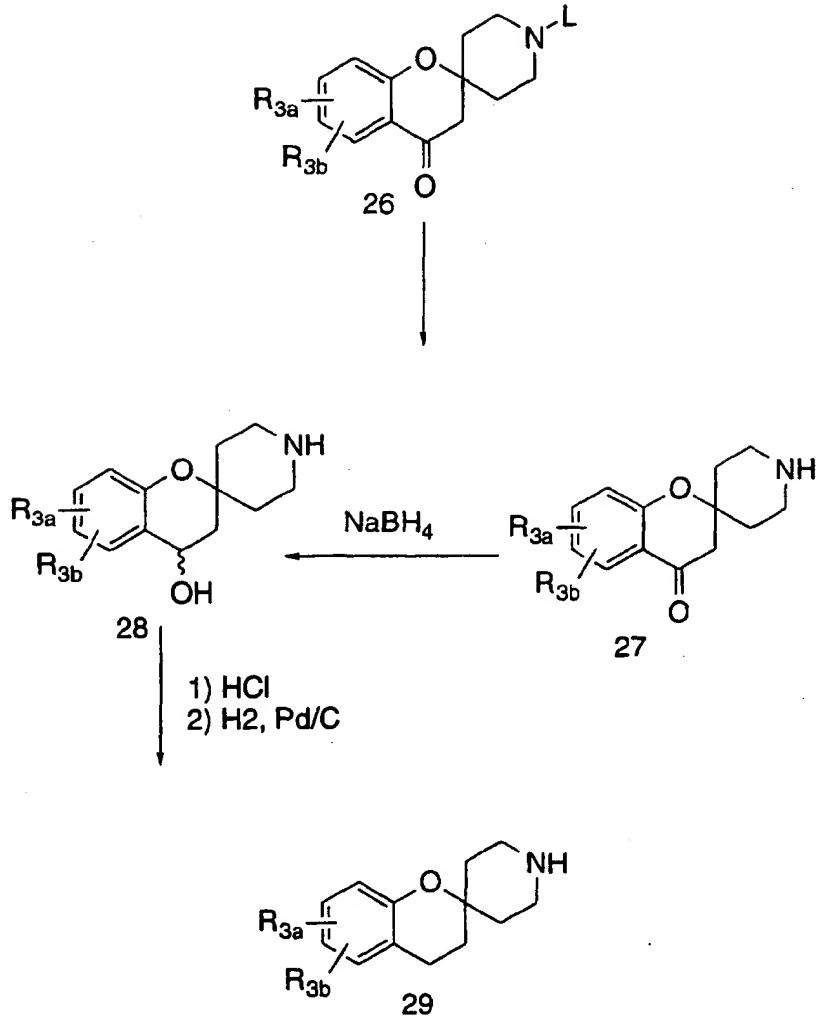
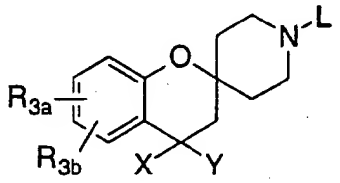


The ring analogs of Formula 26, where X, Y is H,H; OH,H; H,OH; and =O may be prepared by methods described in the literature and known to those skilled in the art. For example, as illustrated in Scheme 13, the spiro[2H-1-benzopyran-2,4'-piperidine] analog can be prepared from a substituted or unsubstituted 2-hydroxyacetophenone and a properly protected 4-piperidone as described by Kabbe, H. J. *Synthesis* **1978**, 886-887 and references cited therein. The 2-hydroxy-acetophenones, in turn, are either commercially available or can be prepared by routes in the literature known to those skilled in the art. Such methods are described by Chang, C. T. *et al., in J. Am. Chem.*

*Soc., **1961**, 3414-3417 and by Elliott, J. M. et al., in J. Med. Chem.* **1992**, 35, 3973-3976. Removal of the protecting group as described in: Protective Groups in Organic Synthesis, Greene, T. W., Wuts, P. G., John Wiley & sons, New York, 1991, and Olofson, R.A. *et al., J. Org. Chem.* **1984**, 49, 2081-2082, provides the amine which then can be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8 shown above which utilize generic intermediate **2**.



26

The ketone functionality in compounds of general structure 27 may be reduced to an alcohol using sodium borohydride or may be fully reduced to a methylene also employing conditions known to those skilled in the art. For example, reduction of the ketone with sodium borohydride, followed by treatment with concentrated hydrochloric acid and hydrogenation yield compounds with general structure 29. The amine of structure 27, 28, or 29 can then be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8 utilizing generic Formula **2**. Alternatively, the ketone can often be reduced after incorporation into the compounds of Formula **I**.

Preparation of chiral hydroxyspiro[2H-1-benzopyran-2,4'-piperidine] analogs can be achieved using optically active reducing agents and the crystallization of diastereomeric salts.

The compounds of Formulas **I** and **II** of the present invention are prepared from a variety of substituted natural and unnatural amino acids such as those of Formulas **30** and **6** and **7** where A is $-(CH_2)_x-C(R_7)(R_{7a})-(CH_2)_y-$. The preparation of many of these acids has been described in the US patent 5206237.

The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art

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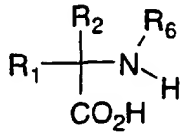
(Williams, R. M. "*Synthesis of Optically Active α-Amino Acids*" Pergamon Press: Oxford, **1989**; Vol. 7). Several methods exist to resolve (DL)-



amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates can be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates can be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* **1989**, *111*, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, some established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* **1986**, *108*, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* **1992**, *114*, 1906; *Tetrahedron Lett.* **1987**, *28*, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* **1991**, *113*, 9276; *J. Org. Chem.* **1989**, *54*, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* **1986**, *108*, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed;

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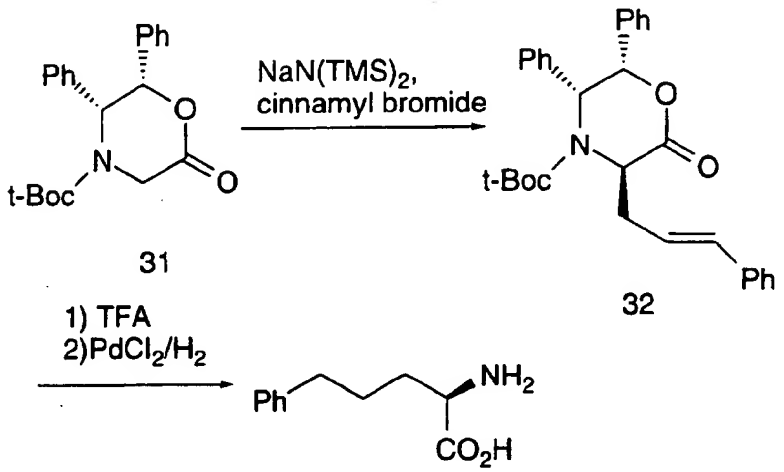
Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 176).

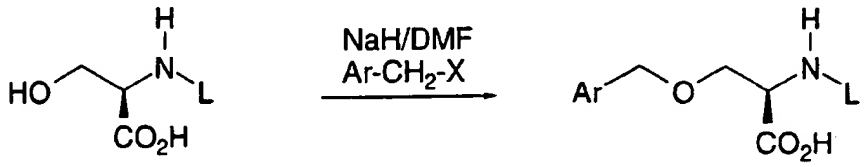
SCHEME 14



31 32 33

For example, alkylation of the enolate of diphenyl-oxazinone **31** (*J. Am. Chem. Soc.* **1991**, *113*, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford **32** which is converted into the desired (D)-2-amino-5-phenylpentanoic acid **33** by removing the N-t-butyloxy-carbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 14).

SCHEME 15



34 35

Intermediates of Formula **30** which are O-benzyl-(D)-serine derivatives **34** are conveniently prepared from suitably

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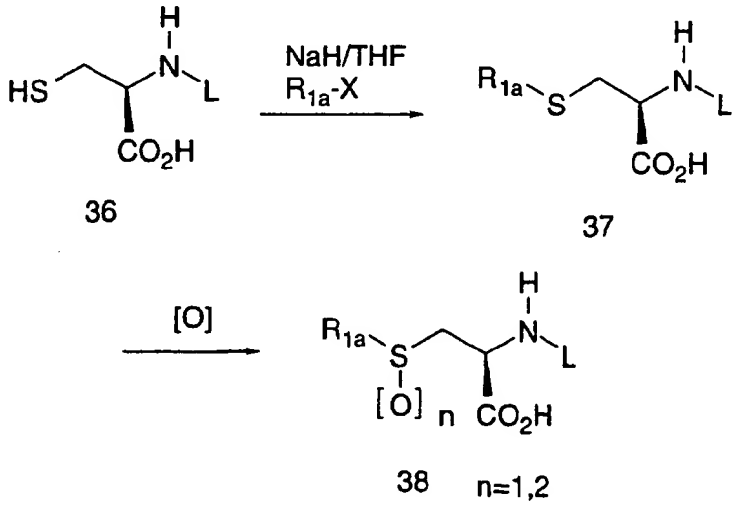
substituted benzyl halides and N-protected-(D)-serine **34**. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of **34** can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* **1989**, 36) as shown in Scheme 15.

The O-alkyl-(D)-serine derivatives are also prepared using the alkylation protocol shown in Scheme 15. Other methods that could be utilized to prepare (D)-serine derivatives of Formula **35** include the acid catalyzed benzylation of carboxyl protected intermediates derived from **34** with reagents of formula $ArCH_2OC(=NH)CCl_3$ (O. Yonemitsu *et al., Chem. Pharm. Bull.* **1988**, *36*, 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* **1991**, *113*, 9276; *J. Org. Chem.* **1989**, *54*, 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 35. In addition D,L-O-aryl(alkyl)serines can be prepared and resolved by methods described above.

SCHEME 16



36 37 38

The alkylation of N-protected-(D)-cysteine **36** is carried out by the procedure described in the (D)-serine derivative synthesis

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and illustrated below with R_{1a}-X where X is a leaving group such as halides and mesyloxy groups as shown in Scheme 16.

The oxidation of the cysteine derivatives **37** to the sulfoxide **38** (n=1) and the sulfone **38** (n=2) can be accomplished with many oxidizing agents. (For a review of the oxidation of sulfides see *Org. Prep. Proced. Int.* **1982**, *14*, 45.) Sodium periodate (*J. Org. Chem.* **1967**, *32*, 3191) is often used for the synthesis of sulfoxides and potassium hydrogen persulfate (OXONE) (*Tetrahedron Lett.* **1981**, *22*, 1287) is used for the synthesis of sulfones.

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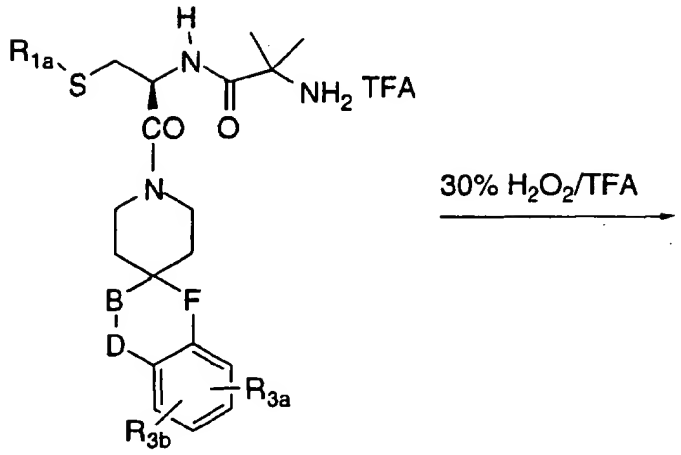
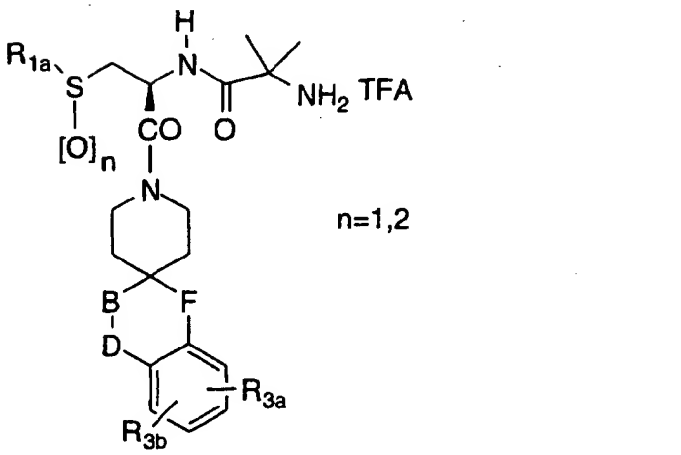
SCHEME 17



39



40

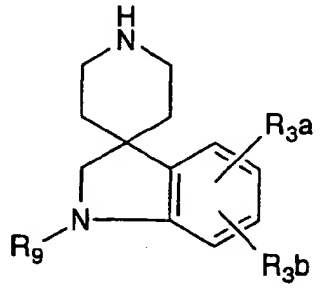
Hence, a variety of substituted amino acids may be incorporated into a growth hormone secretagogue via the chemistry detailed in Schemes 1 and 8. The secretagogues that contain a sulfoxide or a sulfone functional group can also be prepared from the cysteine secretagogues by using sodium periodate or OXONE®. Alternatively hydrogen peroxide may be used as the oxidizing reagent in the last step

of the synthesis as shown in Scheme 17. The sulfoxide **40** (n=1) and sulfone **40** (n=2) analogs can be separated by preparative thin layer chromatography.

Removal of amino protecting groups can be achieved by a number of methods known in the art; as described above and in *Protective Groups in Organic Synthesis* T.W. Greene, John Wiley and Sons, NY. 1981.

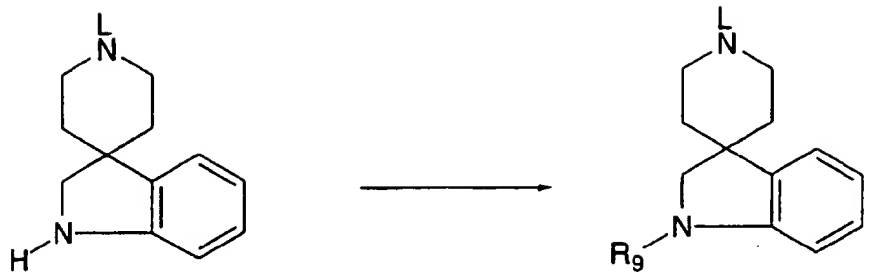
Compounds of Formula **I** wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatogrphy (HPLC) or by recrystallization.

The spiro piperidines of Formula **41** can be prepared by a number of methods, including the syntheses as described below.



41

SCHEME 18

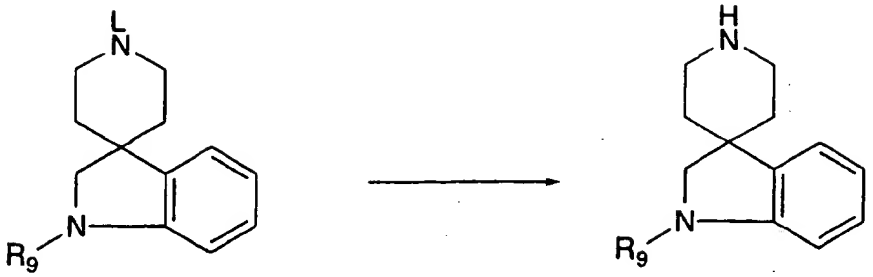


42 43

The spiropiperidines of Formula **42**, wherein L is a defined protecting group, can be synthesized by methods that are known in the literature (for example H. Ong *et al., J. Med. Chem.* **1983**, *23*, 981-986). The indoline nitrogen of **42**, wherein L is a protecting group such as methyl or benzyl, can be reacted by with a variety of electrophiles to yield spiro piperidines of Formula **43**, wherein R9 can be a variety of functionalities. Compound **42** can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent like dichloromethane to yield carbamates, acid chlorides, anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides. Also, the indoline nitrogen of **42** can be reductively alkylated with aldehydes with conditions known in the art. When the aldehyde used in the reductive amination reaction is a protected glyoxylic acid of structure HCOCOOM, wherein M is a defined protecting group, M can be removed from the product and further derivatized. Alternatively, **42** can be reacted with epoxides to produce **43**, wherein R9 is β-hydroxy-substituted alkyl or arylalkyl groups. The indoline **42** can also be transformed to compounds of Formula **43**, wherein R9 = phenyl or substituted phenyl, heteroaryl or substituted heteroaryl, by carrying out the reacting **42** with a fluoro phenyl or fluoro heteroaryl reagent. This

chemistry is detailed in H. Ong *et al., J. Med. Chem.* **1983**, *23*, 981-986.

SCHEME 19



43 44

The spiro piperidine intermediate **43** (L = Me or Bn), wherein R9 is hydrogen or most of the derivatives described above, can be demethylated or debenzylated to produce **44**, wherein R9 is hydrogen or most of the derivatives described above, as shown in Scheme 19. For compounds of Formula **43**, wherein L = Me, demethylation can be carried out by a number methods familiar those skilled in the art. For example, demethylation of **43** be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give **44** by treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of **43** can be effected with the ACE-Cl method as described in R. Olofson *et al., J. Org. Chem.* **1984**, *49*, 2795 and references therein. For intermediates of Formula **43**, wherein L = Bn, removal of benzyl group can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of **43**, L = Bn, can be effected with the ACE-Cl method as described in R. Olofson *et al., J. Org. Chem.* **1984**.

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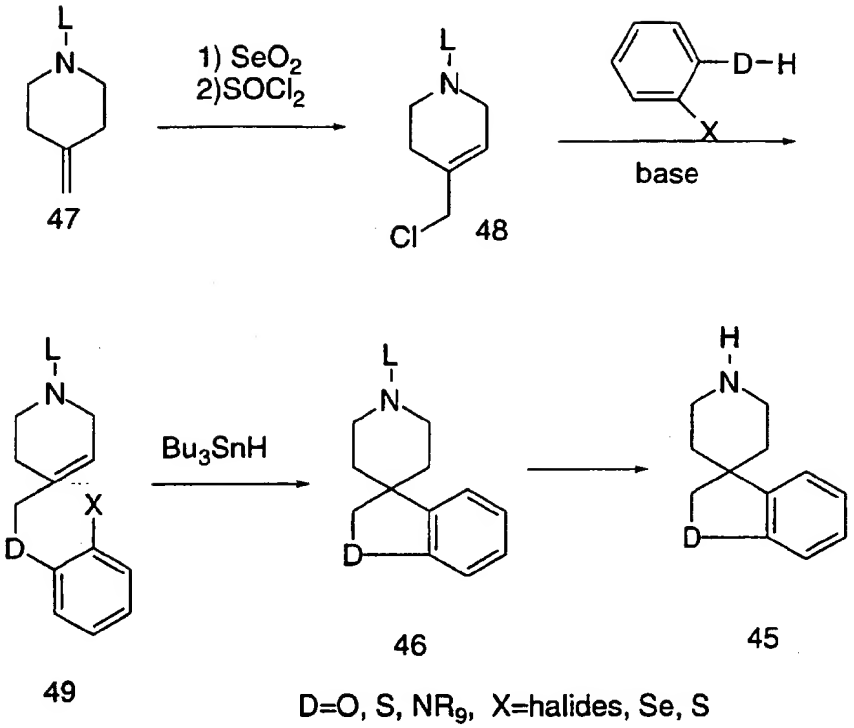
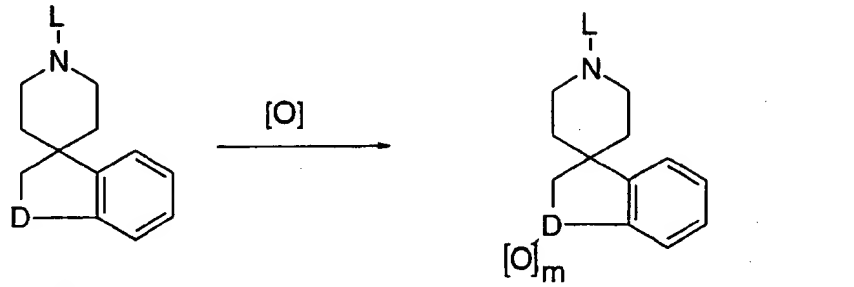
SCHEME 20



The spiro heterocyclic Compounds **45** can be prepared by a number of methods, including the syntheses as described in Scheme 20. Allylic oxidation of the protected piperidine **47** is accomplished by classical methods familiar to those skilled in the art (Rabjohn, N. *Org. React.* **1976**, *24*, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride **48**. When D=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when D=NR9 (R9=H, alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor **49**. When L is a defined protecting group, Compound **49** can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of **49** can be accomplished by reaction with tributyltin hydride (Curran, D. P. *Synthesis* **1988**, 417 and 489) in an inert solvent such as benzene

to yield **46**. Alternatively, Compound **46** (D=NR9) can be prepared by the method shown in Schemes 18 and 19.

SCHEME 21

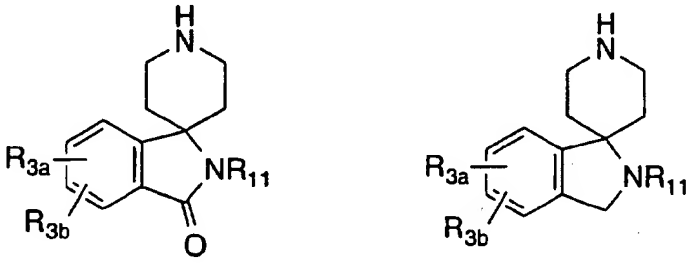


46 D=S

46 D = S(O)$_m$ m=1,2

When D=S, compound **46** can be oxidized to the sulfoxide **47** (n=1) and the sulfone **47** (n=2) by many oxidizing agents (Scheme 21). For example, sodium periodate is often used for the synthesis of sulfoxides and OXONE is used for the synthesis of sulfones. Removal of the protecting group provides the amine **45** which then can be incorporated into a growth hormone secretagogue via the chemistry detaileds in Scheme 1 and 8 shown above which utilize generic intermediate **2.**

SCHEME 22



50 51

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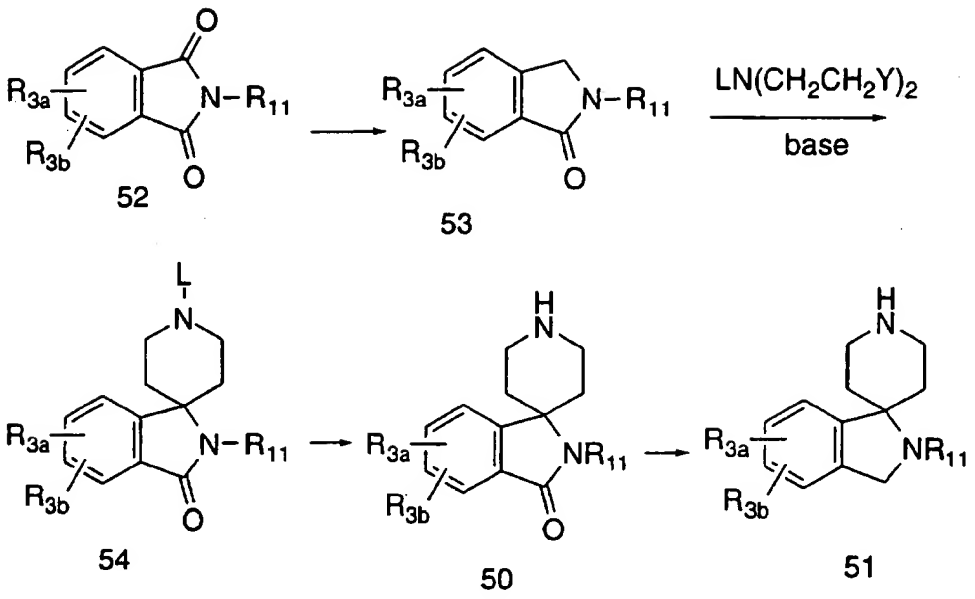

The spiro piperidines of Formula **50** and Formula **51** can be prepared by the syntheses described in Scheme 22.

The phthalimidines of Formula **53**, where R_{11} is defined as alkyl, aryl, $(CH2)_q$-aryl, or a protecting group, are either commercially available or can be synthesized from the corresponding phthalimides by methods that are known in the literature (for example, Bewster *et al.*, in *J. Org. Chem.*, **1963**, *28*, 501; Mcalees *et al.*, *J. Chem. Soc.*, **1977**, 2038). The phthalimidine **53** can be alkylated in the presence of a base, such as potassium hydride, lithium or potassium bis(trimethylsilyl)amide, with the protected bis 2-haloethyl amine, where L is a defined protecting group such as methyl, benzyl, t-BOC, or CBZ, etc., and Y could be Cl, Br, I, to yield the spiropiperidine **54**. The protecting group could be removed by procedures described above to yield Formula **50**. Reduction of the lactam in Formula **50** by hydrides, such as lithium aluminum hydride, yields Formula **51**.

It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

The utility of a compound as a growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay disclosed by Smith , et al., Science, 260, 1640-1643 (1993) (see text of Figure 2 therein).

The instant combination of a bisphosphonate and a growth hormone secretagogue are useful in the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. These diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts, mostly calcium phosphate, pathological hardening of tissues and bone malformations.

2. Conditions which can benefit from a reduction in bone resorption. A reduction in bone resorption should improve the balance between resorption and formation, reduce bone loss or result in bone augmentation. A reduction in bone resorption can aleviate the pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen defficiency, immobilization, glucocorticoid induced and senile), osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcimia, metastatic bone disease, peridontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be aleviated by this treatment.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures may be illustrated by the combination of this invention of bisphosphonates and the growth hormone secretagogues. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases, Trends in Endocrinol. Metab., 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-

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175, clodronate, pamidronate, and BM-210995, a preferred bisphosphonate being alendronate.

The combination of the bisphosphonate, in particular, pamidronate or alendronate, has been found to provide an unexpected effect in the treatment and prevention of diseases involving bone resorption when used in combination with a growth hormone secretagoue. While not being bound to any particular theory of operation, that is, an enhanced effect at reducing and reversing the rate of bone loss that occurs during the aging process, the process known as osteoporosis, is observed with the combination of drugs than would be expected from either drug alone. In particular, combination therapy of a growth hormone secretagogue and a bisphosphonate increase bone mass. This increase in bone mass is possibly a result of increased bone turnover or bone formation produced by elevated growth hormone/IGF-1 levels resulting from the growth hormone secretagogue and decreased bone resorption produced by the bisphosphonate. Such uncoupling of bone formation and bone resorption would not have been predicted based on the disclosures in the art.

A particular illustration of the present invention is the combination in which the bisphosphonic acid active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid). Further exemplifying the present invention is the dosage form thereof containing the sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate (allendronate). Studies indicate that, when parenterally administered, this compound is about five times more effective in reducing hypercalcemia associated with tumor induced bone disease in humans than pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid), the most potent bisphosphonate commercially available for treatment of tumor induced bone disease. 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid and its homologs in which the R^1 side chain is a N-alkyl group varying in length from 1 to 5 carbon atoms and terminally substituted with an amino group may be readily synthesized according to methods disclosed in U.S. Patents 4,407,761, and 4,922,007. In addition to the mono, di,

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and trisodium salts, other pharmaceutically acceptable salts of bisphosphonic acids that may be employed in the present invention include ammonium salts, alkali metal salts such as potassium, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. The salts may be prepared by methods known in the art, such as in U.S. Patent No. 4,922,077.

In the combination of the present invention the bisphosphonate or the growth hormone secretagogue may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of the other agent.

The elements of the combination of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

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The pharmaceutical compositions containing the active ingredient suitable for oral administration may be in the form of discrete units such as hard or soft capsules, tablets, troches or lozenges, each containing a predetermined amount of the active ingredient; in the form of a dispersible powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; in the form of syrups or elixirs; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compounds are admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintergrating agents such as corn starch, or alginic acid; (3) binding agents such as starch, gelatin or acacia; and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastroinestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl disearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108;

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4,160,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients may be

1) suspending agents such as sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia;
(2) dispersing or wetting agents which may be
    (a) a naturally-occuring phosphatide such as lecithin,
    (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene sterate,
    (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol,
    (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or

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(e) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide a palatable oral preparation. These compositions may be prepared by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegatable oil such as olive oil or arachis oils, or a mineral oil such as liquid paraffin or a mixture thereof. Suitable emulsifying agents may be (1) naturally-occuring gums such as gum acacia and gum tragacanth, (2) naturally-occuring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

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Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension or solution. The suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic paternterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspension, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

The combination of this invention may also be administered in the form of suppositories for rectal administration. This composition can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal

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temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene gylcols.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

For topical administration the combination of this invention may be formulated in liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments, jellies or pastes, including tooth-pastes; or solutions or suspensions such as drops, and the like.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance vitamin D_2 and D_3 and hydroxylated derivatives, e.g. 1α-hydroxy-vitamin D_3, 1α-hydroxy-vitamin D_2, 1α-25-dihydroxy-vitamin D_3, 1α-25-dihydroxy-vitamin D_2, calcitonin (human, porcine or salmon), mitra-mycin, sodium fluoride, estrogens, and non-steroid antiinflammatory drugs, e.g. acetylsalicyclic acid, indomethacin, naprosyn, and timegadine.

The dosage of the active ingredients in the compositions of this invention may be varied. However, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration and on the duration of the treatment. Generally, dosage levels of the bisphosphonate of between 0.001 and 10 mg/kg of body weight, preferably between about 0.01 and 1.0 mg/kg are administered. Dosage levels of the growth hormone secretatogoue of between 0.0001 to 25 mg/kg of body weight daily are administered to patients to obtain effective treatment or prevention of osteoporosis.

The instant combination may also be administered on an intermittent basis. For the treatment or prophylaxis of diseases involving bone resorption a typical primary oral dose of bisphosphonate which lies within the range of from about 0.001 mg to 10 mg per kg body weight and a dose of growth hormone secretatogoue of between 0.0001 to 25 mg per kg of body weight may be administered and then,

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if necessary a sustaining dose of one element or both elements approximately equal to half of the primary dose may be administered at weekly, semiweekly, semimonthly, monthly, bimonthly, quarterly, semiannual, annual or biannual intervals.

The preferred compounds of this combination product are prepared by the following examples. Full descriptions of the preparation of growth hormone secretagoues are also found in U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/13696; and Science, 260, 1640-1643 (June 11, 1993).

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the spirit or scope of the present invention.

EXAMPLE 1

A mixture of 1 mole of 4-aminobutyric acid, 1.5 moles of phosphoric acid and 500 cc anhydrous chlorobenzene, is heated up to 100°C. At this temperature, phosphorus trichloride in the amount of 1.5 mole is added under strong stirring. The mixture is stirred at 100°C for 3 hours until the dense phase is completely formed and is then allowed to cool. The solid is filtered, washed with a small amount of chlorobenzene and dissolved in water. The solution is heated to the boiling point for one hour, it is then cooled and decolorized with active carbon. The material is filtered and the product is precipitated with an excess of hot methanol. The crude material so obtained is heated under reflux for eight hours in 20% hydrochloric acid. The hydrochloric acid is removed by distillation and the residue is recrystallized from water. The product is 4-amino-1-hydroxybutan-1,1-bisphosphonic acid in the form of a white crystalline powder which has the structure hereinbelow as shown by the properties also reported hereinbelow:

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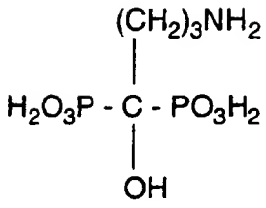

Elementary analysis

	C %	H %	N %	P %
Found	17.88	5.62	4.93	23.94
Calcd for Product	19.28	5.26	5.64	24.86
Calcd for product as monohydrate	17.98	5.66	5.24	23.19

EXAMPLE 2

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,

Step A: 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 9.22 g (45.6 mmol) of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) in 30 mL methanol was hydrogenated at 40 psi in the presence of 1.0 g of 5% Pt/C for 4.5 hours. Celite was added and the mixture filtered through a pad of Celite. The filtrate was concentrated and allowed to stand for 16 hours at room temperature which resulted in formation of crystals. The material was isolated by filtration and dried under vacuum to afford 4.18 g (23.7 mmol, 52%) of the product. The mother liquors were diluted to 100 mL with methanol, treated with 2 g of charcoal, filtered

through Celite and the filtrate concentrated under vacuum to approximatley 15 mL. A second crop formed yielding 2.02 g of product (11.5 mmol, 25%). Another recycling of the mother liquors afforded a third crop of 0.88 g (5.0, 11%). A total of 7.08 g (40.2 mmol, 88%) of the product was thus obtained.

^{1}H NMR (200 MHz, $CDCl_3$): 1.6 (br s, 2H), 1.80 (m, 1H), 2.55 (m, 2H), 2.88 (m, 1H), 3.42 (dd; 7Hz, 11Hz; 1H), 6.98 (d, 8Hz, 1H), 7.2 (m, 3H), 8.3 (br s, 1H).

FAB-MS: calculated for $C_{10}H_{12}N_2O$ 176; found 177 (M+H, 100%).

Step B: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

2.37 g (13.5 mmol) of 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) and 2.02 g (13.5 mmol) of L-tartaric acid were suspended in 40 mL of ethanol. The mixture was gently heated and complete dissolution achieved by dropwise addition of 5 mL of distilled water. The solution was cooled to room temperature and aged overnight. The solid that formed was removed by filtration, washed with ethanol/diethyl ether (1:1) and dried under vacuum to afford 1.75 g of crude L-tartrate salt. The mother liquors were evaporated to dryness under vacuum, redissolved in 40 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (6x20 mL) and the combined extracts washed with water (1x) and brine (1x), dried over potassium carbonate, filtered and solvents removed under vacuum to afford 1.29 g (7.33 mmol) of partially enriched 3(R) amine.

The original 1.75 g batch of L-tartrate salt was recrystallized twice from aqueous ethanol to afford 1.03 g (3.17 mmol, 24%) of purified L-tartrate salt with $[a]_D=-212°$ (c=1, H_2O). The purified L-tartrate salt was dissolved in 20 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (5x10 mL); combined extracts were washed with water and brine then dried over potassium carbonate, filtered and solvents removed under vacuum to afford 522 mg (2.96 mmol, 22% overall) of the 3(S) amine, $[a]_D=-446°$ (c=1,CH_3OH).

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The remaining 1.29 g (7.33 mmol) of partially enriched 3(R) amine was treated with 1.10 g (7.33 mmol) of D-tartaric acid as described above and the resulting salt recrystallized twice from aqueous ethanol to afford 1.20 g of purified D-tartrate salt, $[a]_D=-214°$ (c=1,H_2O). The purified D-tartrate salt was dissolved in 20 mL of water and the free base isolated as described above to give 629 mg (3.57 mmol, 26% overall) of the 3(R) amine, $[a]_D=+455°$ (c=1,CH_3OH).

Step C: 2,2-Dimethylbutanedioic acid, 4-methyl ester

2,2-dimethylsuccinic acid (20 g, 137 mmol) dissolved in 200 mL absolute methanol at 0°C was treated dropwise with 2 mL concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 hours.

The mixture was concentrated *in vacuo* to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed *in vacuo*. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of a viscous oil that slowly solidified upon standing. ^1H NMR analysis indicates the product is a mixture of the title compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200 MHz, $CDCl_3$) of title compound: 1.29 (s, 6H), 2.60 (s, 2H), 3.66 (s, 3H). NMR (200 MHz, $CDCl_3$) of isomer: 1.28 (s, 6H), 2.63 (s, 2H), 3.68 (s, 3H).

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Step D: 3-[Benzyloxycarbonylamino]-3-methylbutanoic acid, methyl ester

To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester (Step C), containing 15% of the isomeric 1-methyl ester compound, in 150 mL benzene was added 13 mL of triethylamine (9.4 g, 93 mmol, 1.01 eq) followed by 21.8 mL diphenylphosphoryl azide (27.8 g, 101 mmol, 1.1 eq). The mixture was heated under nitrogen at reflux for 45 minutes then 19 mL (19.9 g, 184 mmol, 2 eq) of benzyl alcohol was added and refluxing continued for 16 hours.

The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL ethyl acetate, washed with water (1x), saturated aqueous sodium bicarbonate (2x) and brine (1x). The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume *in vacuo*. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27 g (68.9 mmol, 75%) of the title compound as a pale yellow liquid in addition to a small amount of pure 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester. ^{1}H NMR (200MHz, $CDCl_3$) of title compound: 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H). ^{1}H NMR (200 MHz, $CDCl_3$) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200 MHz, $CDCl_3$): 1.19 (s, 6H), 3.30 (d, 7Hz, 2H; resonance collapses to singlet in CD_3OD), 3.67 (s, 3H), 5.09 (s, 2H), 5.22 (br s,1H; resonance not observed in CD_3OD), 7.3 (br s, 5H).

Step E: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27 g (68.9 mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Step D) in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2N NaOH (102 mmol, 1.5 eq). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to

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0°C and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26 g (68.7 mmol, 99%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

Step F: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 252 mg (1.43 mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Step B) in 4 mL of methylene chloride at room temperature was added 400 mg (1.60 mmol, 1.1 eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid (Step E) followed by 760 mg (1.7 mmol, 1.2 eq) benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro-phosphate and 0.50 mL of diisopropylethylamine (380 mg, 2.9 mmol, 2 eq). After 3 hours at room temperature, the mixture was diluted into 30 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 586 mg (1.43 mmol, 100%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.82 (m, 1H), 2.52 (s, 2H), 2.5-3.0 (m, 3H), 4.51 (m, 1H), 5.07 (br s, 2H), 5.57 (br s, 1H), 6.68 (d, 7Hz, 1H), 6.97 (d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.61 (br s, 1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H, 100%); $[a]_D$=+137° (c=1, $CHCl_3$).

Step G: 5-Phenyltetrazole

Zinc chloride (3.3 g, 24.3 mmol, 0.5 eq) was added to 15 mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0 g of benzonitrile (48.5 mmol, 1.0 eq) followed by 3.2 g of sodium azide (48.5 mmol, 1.0 eq). The

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heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30 mL) was added and the mixture acidified by the addition of 5.1 mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15 mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38 g (43.7 mmol, 90%) of the product.

Step H: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0 g (34.2 mmol) of 5-phenyltetrazole in 55 mL of acetone was added 5.0 mL of triethylamine (3.6 g, 35.6 mmol, 1.04 eq). After 15 minutes, a solution of 10.0 g of triphenylmethyl chloride (35.9 mmol, 1.05 eq) in 20 mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour. Water (75 mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75 mL of water and dried at 60°C under vacuum to give 13.3 g (34.2 mmol, 100%) of the product.

Step I: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole

A solution of zinc chloride (6.3 g, 46.2 mmol, 0.6 eq) in 35 mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0 g, 77.3 mmol, 1.0 eq) was dissolved in 300 mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5 mL of 1.6 M n-butyllithium in hexane (80.0 mmol, 1.05 eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature.

In a separate flask, 4-iodotoluene (20.17 g, 92.5 mmol, 1.2 eq) and bis-(triphenylphosphine)nickel (II) dichloride (1.5 g, 2.3 mmol, 0.03 eq) were dissolved in 60 mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5 mL of 3.0 M solution of methylmagnesium

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chloride in tetrahydrofuran (4.5 mmol, 0.06 eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10 mL of glacial acetic acid (1.6 mmol, 0.02 eq) in 60 mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150 mL of 80% saturated aqueous sodium chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150 mL of 80% saturated aqueous sodium chloride buffered to pH>10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to approximately 50 mL then 250 mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50 mL and acetonitrile added to make the final volume 150 mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50 mL of cold acetonitrile followed by 150 mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0 g (62.8 mmol, 81%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Step J: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole

A solution of 3.15 g (6.6 mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole (Step I) in 25 mL of methylene chloride was treated with 1.29 g (7.25 mmol, 1.1 eq) of N-bromo-succinimide, 80 mg (0.5 mmol, 0.07 eq) of AIBN, 200 mg of sodium acetate and 200 mg of acetic acid. The mixture was heated at reflux for 2 to 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued

until almost all the methylene chloride was removed the the total volume reduce to approximately 12 mL and 12 mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81g (5.04 mmol, 76%) of the product. ^1H NMR (200 MHz, $CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step K: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 437 mg (1.07 mmol) of the intermediate obtained in Step F in 2 mL of dry dimethylformamide at room temperature under nitrogen was added 55 mg of 60% sodium hydride oil dispersion (33 mg NaH, 1.38 mmol, 1.3 eq). After 15 minutes, a solution of 715 mg (1.28 mmol, 1.2 eq) N-triphenyl-methyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole (Step J) in 1.5 mL of dry dimethyl-formamide was added and the mixture stirred for 90 minutes.

The reaction mixture was added to 100 mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1), afforded 902 mg (1.02 mmol, 95%) of the product. ^1H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.68 (m, 1H), 2.2-2.5 (m, 5H), 4.44 (m, 1H), 4.67 (d, 14Hz, 1H), 5.06 (s, 2H), 5.12 (d, 14Hz, 1H), 5.63 (br 1, 1H), 6.65 (d, 8Hz, 1H), 6.9-7.5 (m, 31H), 7.85 (m, 1H).

Step L: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

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A solution of 902 mg (1.02 mmol) of the intermediate obtained in Step H in 5 mL methanol was hydrogenated at room temperature and one atmosphere over 160 mg of 20% $Pd(OH)_2/C$ for 14 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) to afford 568 mg (0.91 mmol, 89%) of the title compound. ^1H NMR (200 MHz, CD_3OD): 1.33 (s, 3H), 1.37 (s, 3H), 2.0-2.6 (m, 6H), 4.35 (dd; 7, 11 Hz; 1H), 4.86 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.00 (d, 8 Hz, 2H), 7.15-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H, 100%).

EXAMPLE 3

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

Step A: 3-[(2-(R)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate (Example 1) and (R)-2-benzyloxlpropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett., 26, 1261-1264 (1985) by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step A. ^1H NMR (200MHz, CD_3OD): 1.25 (d, 6Hz, 3H), 1.35 (s, 6H), 2.11 (m, 1H), 2.32 (m, 1H), 2.5-2.7 (m, 4H), 2.95 (m, 1H), 3.17 (m, 1H), 3.80 (m, 1H), 4.40 (m, 1H), 4.44 (d, 11Hz, 1H), 4.64 (d, 11Hz, 1H), 4.90 (d, 15Hz, 1H), 5.02 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.1-7.7 (m, 15H).

FAB-MS: calculated for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H, 100%).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step B. ^1H NMR (400MHz, CD_3OD): 1.22 (d, 6Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.31 (m, 1H), 2.45-2.70 (m, 4H), 2.81 (dd; 10, 12Hz; 1H), 3.08 (dd; 4, 12Hz; 1H), 3.92 (m, 1H), 4.36 (dd; 7, 11Hz; 1H), 4.93 (d, 15Hz, 1H), 5.17 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.19 (d, 8Hz, 2H), 7.20-7.35 (m, 4H), 7.54 (m, 2H), 7.65 (m, 2H). FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H, 45%).

EXAMPLE 4 (METHOD 1)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Step A: 1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine]hydrochloride

To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described by H. Ong, et al., J. Med. Chem., 23, 981-986 (1983)) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed

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under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%).
^{1}H NMR ($CDCl_3$, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-propanamide

To 0.35g (1.15 mmol) of (2R)-2-[(1,1-dimethylethoxy)-carbonyl]amino-3-[2-(phenylmethyloxy)ethyl]-1-propanoic acid in 13 mL of dichloromethane was added 1,2-dihydro-1-methanesulfonylspiro-[3H-indole-3,4'-piperdine] hydrochloride (0.325 g; 1.07 mmol), 0.18 mL (1.63 mmol) of N-methylmorpholine, 0.159 g (1.18 mmol) of 1-hydroxybenztriazole(HOBT) and stirred for 15 min. EDC (0.31 g; 1.62 mol) was added and stirring was continued for 1h. An additional 60 µL of N-methylmorpholine was added and stirred for 45 min. The reaction mixture was poured into 5 mL of water and the organic layer was separated. The organic layer was washed with 5 mL of 0.5N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate

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solution. The combined organics were dried over anhydrous magnesium sulfate, and concentrated to yield 0.627 g of the product as a yellow foam which was used without purification.

To a 0.627 g (1.07 mmol) of the above product in 5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 75 min. An additional 1.00 mL of trifluoroacetic acid was added and stirred for 10 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified by pouring into 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give the 0.486 g of the amine as a light yellow foam which was used without purification.

To 0.486 g (1.01 mmol) of the amine and 10 mL of dichloromethane was added 0.26g (1.28 mmol) of 2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanoic acid, 0.173 g (1.28 mmol) of 1-hydroxybenztriazole (HOBT) and EDC (0.245 g; 1.28 mol) and stirried at RT overnight. The reaction mixture was poured into 5.0 mL of water and the organic layer was separated. The aqueous layer was back extracted with 5 mL of dichloromethane. The combined organics were washed with 5.0 mL of 0.5N aqueous hydrochloric acid, 5 mL of saturated aqueous sodium bicarbonate solution dried over anhydrous magnesium sulfate, and concentrated to yield 0.751 g of the crude product as a yellow foam. A solution of this crude product in dichloromethane was chromatographed on 25 g of silica gel and eluted first with hexanes/acetone/dichloromethane (70/25/5) and then with hexanes/acetone/dichloromethane (65/30/5). This gave 0.63 g of the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86

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(s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To 0.637 g (0.101 mmol) of the intermediate from Step B in 5 mL of dichloromethane was added 2.5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated to an oil, taken up in 10 mL of ethyl acetate and washed with 8 mL of 10% aqueous sodium carbonate solution. The aqueous layer was further extracted with 5 mL of ethyl acetate. The combined organics were washed with 10 mL of water, dried over magnesium sulfate, filtered and concentrated to give the 0.512 g of the free base as a white foam.

To 0.512 g of the free base in 5 mL of ethyl acetate at 0°C was added 0.2 mL of saturated hydrochloric acid in ethyl acetate and stirred for 1.5 h. The white precipitate was filtered under nitrogen, washed with ether, and dried to give 0.50 g of the title compound as a white solid

^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 5 (METHOD 2)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

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Step A: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethoxy)ethyl]-1-propanoic acid allyl ester

Prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-(phenylmethyloxy)ethyl-propanoic acid and allyl alcohol by carrying out the coupling reaction in CH_2Cl_2 in the presence of EDC and DMAP.

^1H NMR (400MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid

To a stirred solution of the crude intermediate obtained in Step A (6.[illegible], 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.

^1H NMR (400Hz, CD_3OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanamide

To a solution of 1.0 g (3.44 mmol) of 1-methanesulfonyl-spiro[indoline-3,4'-piperidine] hydrochloride, 1.44 g (3.78 mmol) of

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(2R)-[[-2-(1,1-dimethylethoxy)carbonyl)amino]-2,2-dimethyl-1-oxo-ethyl]-amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid, N-methyl morpholine (0.58 mL; 5.20 mmol), and 1-hydroxybenztriazole (HOBT) (0.58 g; 3.78 mmol), in 50 mL of dichloromethane was added EDC (1.03 g; 5.20 mmol) and stirred at RT for 16h. The reaction mixture was diluted with an additional 50 mL of dichloromethane and washed with aqueous sodium bicarbonate solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography (50 g silica gel) of the crude oily residue gave 2.148 g (90%) of the desired material as a colorless foam.

^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 2.148 g (3.41 mmol) of the intermediate from Step C in 10 mL of dichloromethane was added 5 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated and basified with 100 mL of 5% aqueous sodium carbonate solution and extracted with dichloromethane (3X50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield a colorless foam. To a solution of the foam in 25 mL of ethyl acetate at 0°C was added 4 mL of 1M solution of hydrochloric acid in ethyl acetate. The precipitate was filtered and washed first with ethyl acetate and then with ethyl acetate-ether (1:1), dried to yield 1.79 g (93%) of the title compound as a colorless solid.

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^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 6

N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-[3-phenylpropyl]-2-amino-2-methyl-propanamide hydrochloride

Step A: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanamide

The title compound was prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]amino-4-phenyl-1-butanoic acid and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine] hydrochloride by using the coupling method as described in Example 18, Step B. The crude product was purified on silica gel using 5% Acetone in CH_2Cl_2.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.2 (m, 9H), 4.9 (m, 1H), 4.5 (m, 1H), 3.8 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 2H), 2.3 (s, 2H), 2.0 (m, 2H), 1.7 (m, 4H), 1.5 (s, 6H), 1.4 (s, 9H).

Step B: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

Prepared from the intermediate obtained in step A using the deprotection method as described in Example 18, Step C.

^{1}H NMR (400MHz, CD_3OD) δ 7.3 (m, 9H), 4.5 (m, 1H), 3.9 (m, 2H), 3.5 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 4H), 2.0 (m, 4H), 1.6 (s, 6H).

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EXAMPLE 7

Combined Therapy with N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide and Pamidronate: Exploratory Nine(9)-Week Bone Study in Old Female Rats

The purpose of this study was to evaluate the effect of N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide, alone and in combination with pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid), on the bone in old female rats. The duration of the study was 9 weeks. The frequency of dosing with N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide was once daily, seven days a week. The frequency of dosing with pamidronate was once a week, on the first day of the week. The route of administration of N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide was by gavage. The control article was distilled water and the carrier was distilled water. The dosing volume of N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide was 5 ml/kg, and the dosing volume of pamidronate was 1 ml/kg. The test system was the female rat of a strain Sprague-Dawley Crl:CD® (SD) BR, which were of an approximate age at the start of the study of greater than 18 months, and which were of an approximate weight at the start of the study of 300-400 g.

There were no contaminants in the feed and water that are known to interfere with the purpose and conduct of this study. There were no contaminants in the bedding that are known to interfere with the purpose and conduct of this study. The rats were housed in individual stainless steel wire cages.

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Dosage levels	Dose code	Number of animals Males	Females
Control 1	01	0	7
Control 2 Distilled water	07	0	8
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide [50 mg/kg/day]	15	0	11
Pamidronate [120 µg/kg/once a week]	25	0	10
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide + Pamidronate [50 mg/kg/day + 120 µg/kg/once a week]	35		12

HORMONE ANALYSIS

Drug Day 1: Blood sampling (approximately 1.5 ml) was from orbital sinus on non-fasted rats, all groups, for measurements of GH; bleeding was done 15 minutes post dosing in control groups and groups receiving N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide alone or in combination.

Drug Weeks 2*, 9:

Blood sampling (approximately 1.5 ml) was from orbital sinus on non-fasted rats, all groups except control group 1, for measurement of GH; bleeding was done 15 minutes post dosing in

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control group 2 and groups receiving N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide alone or in combination; Blood sampling (volume: as much as possible) was from cava at necropsy, on non-fasted rats, all groups for measurement of IGF-1. (* for control group 1, only)

Growth Hormone Levels (Day 1)

Control 1	10 ng/ml
Control 2	10 ng/ml
Pamidronate	5 ng/ml
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide	85 ng/ml
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide + Pamidronate	48 ng/ml

BONE LABELING

All rats received bone labelling agents (oxytetracycline and calcein): 9 days (oxytetracycline) and 2 days (calcein), before necropsy.

Oxytetracycline was injected subcutaneously twice (2 injections approximately 5 hours apart) at a dose level of 25 mg/kg, and calcein was injected intraperitonally at a dose level of 15 mg/kg.

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EFFECT ON OSTEOBLAST SURFACE

Treatment	% Osteoblast Surface (± SEM)
Control 2	3.51 (0.63)
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide	3.91 (0.73)
Pamidronate	0.80 (0.26)
N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide + Pamidronate	3.05 (0.36)

As the results indicate, the growth hormone secretagogue restored bone formation that had been suppressed by the bisphosphonate pamidronate to control levels. In addition, there was no difference in osteoclast surface (bone resorption) as a result of treatment with the growth hormone secretagogue. The results observed in this study are intended to be representative of the unexpected benefits that may be realized with the instant invention.

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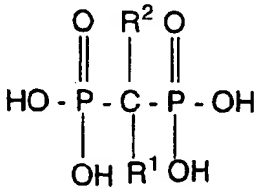
While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A combination useful for the treatment of osteoporosis which comprises a bisphosphonate and a growth hormone secretagogue.

2. The combination of Claim 1 wherein the bisphosphonate is of the Formula X:



X

wherein:

R^1 is selected from the group consisting of:

(a) C_{1-5} alkyl, unsubstituted or substituted with:
  (1) NH_2,
  (2) pyridyl,
  (3) pyrrolidyl,
  (4) NR^3R^4
(b) NR^5,
(c) SR^6, and
(d) Cl;

R^2 is H, OH, or Cl;

R^3 is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-10} alkyl; and

R^6 is aryl;

or a pharmaceutically acceptable salt thereof.

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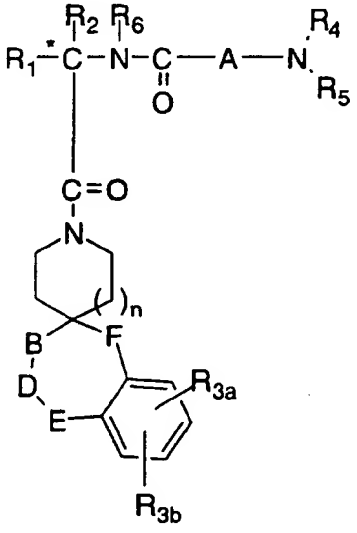
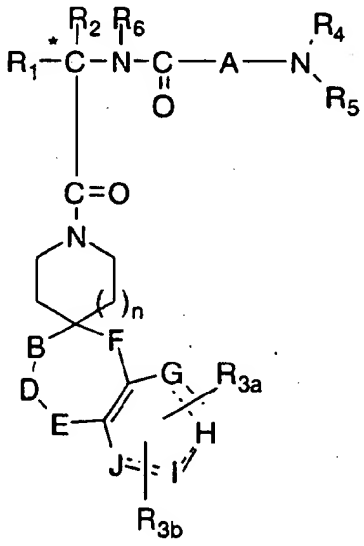
3. The combination of Claim 1 wherein the bisphosphonate is selected from alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid;
or a pharmaceutically acceptable salt thereof.

4. The combination of Claim 3 wherein the bisphosphonate is alendronic acid or a pharmaceutically acceptable salt thereof.

5. The combination of Claim 1 wherein the growth hormone secretagogue is of the Formula I or II:



Formula I



Formula II

wherein:
R_1 is selected from the group consisting of:
-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),
-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl,
-aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),
-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, $OC(O)$, $C(O)O$, or $-CR_2=CR_2-$, or $-C\equiv C-$,
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, $-C_1$-C_6 alkyl, $-OR_2$, cyano, $-OCF_3$, methylenedioxy, nitro, $-S(O)_mR$, $-CF_3$ or $-C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, $-C_1$-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $-S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form $-(CH_2)_rL_a(CH_2)_s-$ where L_a is $-C(R_2)_2-$, $-O-$, $-S(O)_m-$, or $-N(R_2)-$, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

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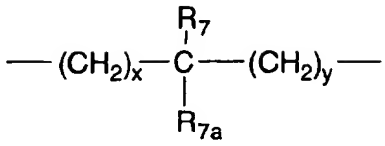
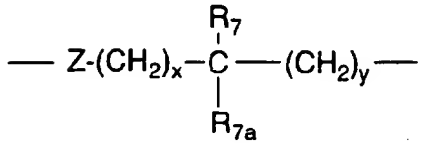
A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=0, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-,

or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m$$R_{2a}$, -C(O)N$HSO_2$($CH_2$)q-aryl, -$SO_2$NHC≡N, -$SO_2$NHC(O)$R_{2a}$, -$SO_2$NHC(O)($CH_2$)$_q$aryl, -N($R_2$)C(O)N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)N($R_{2a}$)($CH_2$)$_q$-aryl, -N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)$R_{2a}$, -N($R_{2a}$)C(O)($CH_2$)q aryl, -OC(O)N($R_{2a}$)($R_{2a}$), -OC(O)N($R_{2a}$)($CH_2$)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;

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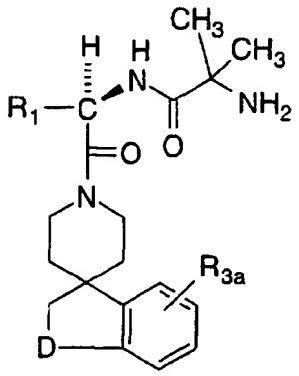
and pharmaceutically acceptable salts and individual diastereomers thereof.

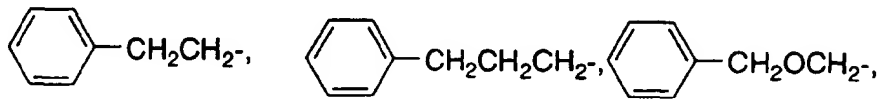
6. The combination of Claim 1 wherein the growth hormone secretagogue is of the Formula V:

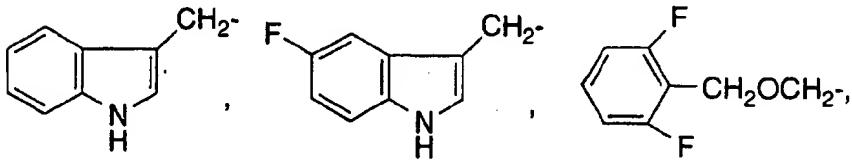


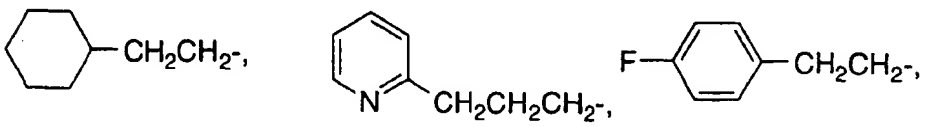
V

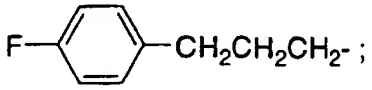
wherein:

R_1 is selected from the group consisting of:





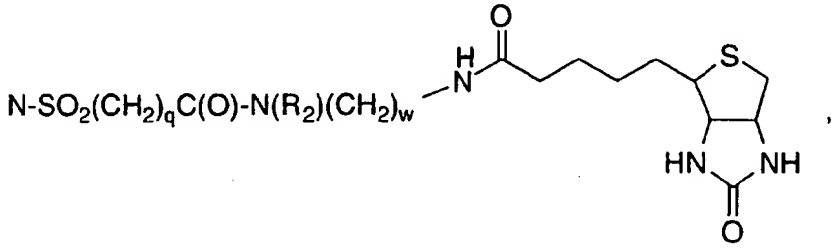


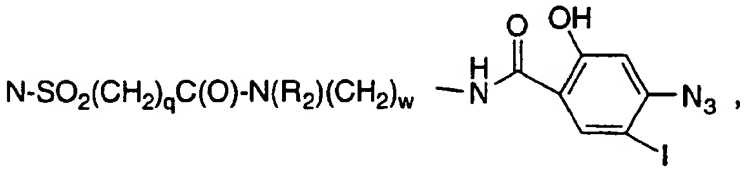


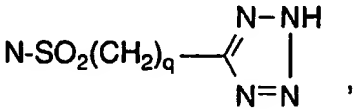
R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)$_m$-, N(R_2), NSO$_2$(R_2), NSO$_2$(CH$_2$)$_t$aryl, NC(O)(R_2), NSO$_2$(CH$_2$)$_q$OH, NSO$_2$(CH$_2$)$_q$COOR_2, NSO$_2$(CH$_2$)$_q$C(O)-N(R_2)(R_2), N-SO$_2$(CH$_2$)$_q$C(O)-N(R_2)(CH$_2$)$_w$OH,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

7. The combination of Claim 1 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

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17) N-[1(R)-[(1,2-dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

8. The combination of Claim 1 wherein the bisphosphonate is alendronic acid, or pamidronic acid, or a pharmaceutically acceptable salt thereof, and the growth hormone secretagogue is:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

or a pharmaceutically acceptable salt thereof.

9. The combination of Claim 1 wherein the bisphosphonate is alendronic acid, or a pharmaceutically acceptable salt thereof, and the growth hormone secretagogue is:

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for the treatment of osteoporosis which comprises a combination of a bisphosphonate and a growth hormone secretagogue, in conjunction with an inert carrier.

11. The composition of Claim 10 wherein the bisphosphonate is of the Formula X:

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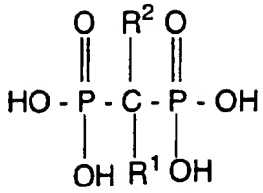

X

wherein:

R^1 is selected from the group consisting of:

(a) C_{1-5} alkyl, unsubstituted or substituted with:
  (1) NH_2,
  (2) pyridyl,
  (3) pyrrolidyl,
  (4) NR^3R^4
(b) NR^5,
(c) SR^6, and
(d) Cl;

R^2 is H, OH, or Cl;

R^3 is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-10} alkyl; and

R^6 is aryl;

or a pharmaceutically acceptable salt thereof.

12. The composition of Claim 10 wherein the bisphosphonate is selected from alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid;
or a pharmaceutically acceptable salt thereof.

13. The composition of Claim 12 wherein the bisphosphonate is alendronic acid or a pharmaceutically acceptable salt thereof.

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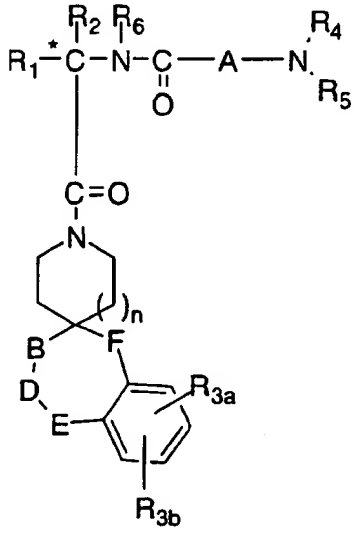
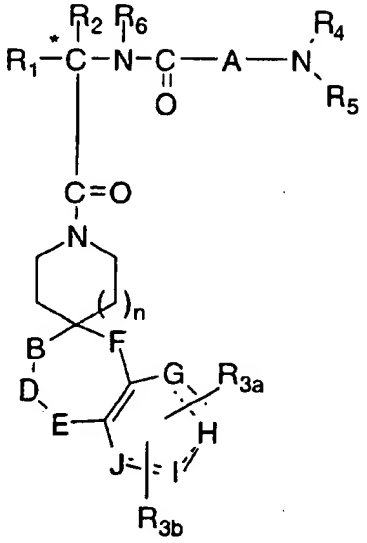
14. The composition of Claim 10 wherein the growth hormone secretagogue is of the Formula I or II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:
-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),
-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl,
-aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),
-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),
wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or -C≡C-,
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;
R_2 is selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

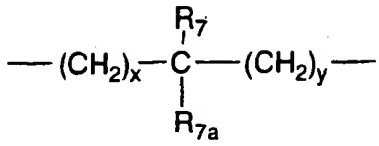
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

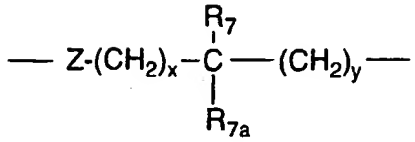
R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=0, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

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R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m$$R_{2a}$, -C(O)NH$SO_2$($CH_2$)q-aryl, -$SO_2$NHC≡N, -$SO_2$NHC(O)$R_{2a}$, -$SO_2$NHC(O)($CH_2$)$_q$aryl, -N($R_2$)C(O)N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)N($R_{2a}$)($CH_2$)$_q$-aryl, -N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)$R_{2a}$, -N($R_{2a}$)C(O)($CH_2$)q aryl, -OC(O)N($R_{2a}$)($R_{2a}$), -OC(O)N($R_{2a}$)($CH_2$)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

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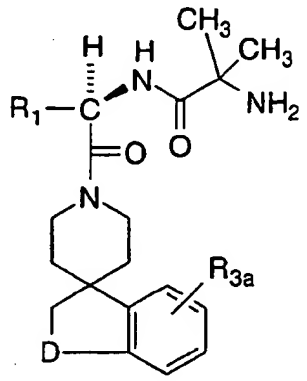
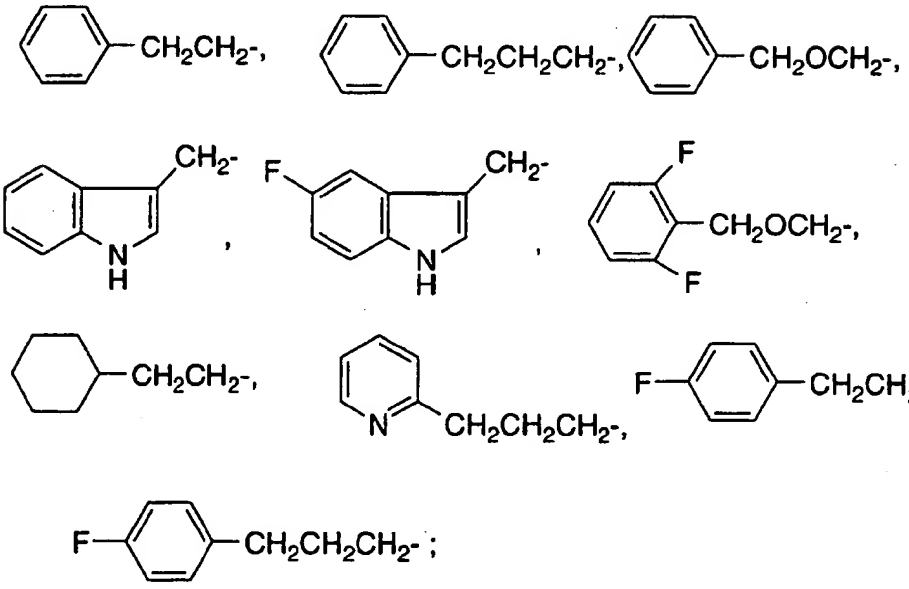
15. The composition of Claim 10 wherein the growth hormone secretagogue is of the Formula V:



V

wherein:

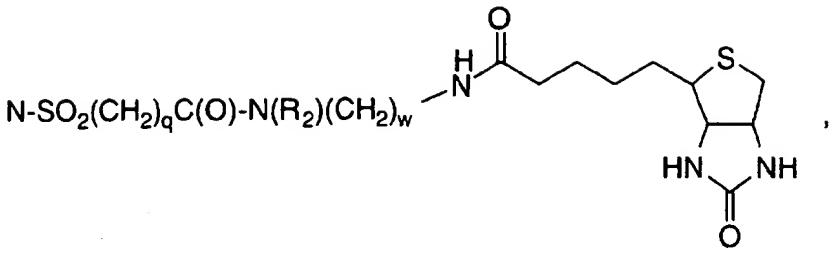
R_1 is selected from the group consisting of:

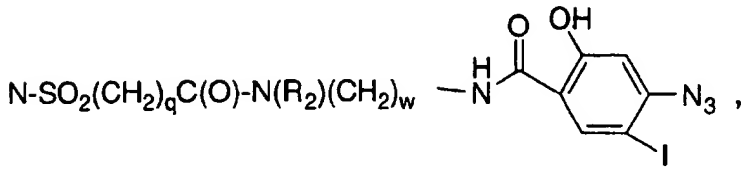


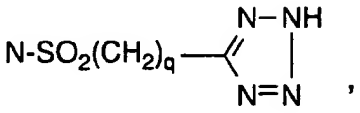
R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)m-, N(R2), $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $NSO_2(CH_2)_qC(O)$-$N(R_2)(R_2)$, N-$SO_2(CH_2)_qC(O)$-$N(R_2)(CH_2)_wOH$,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

16. The composition of Claim 10 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

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2) N-[1(R)-[(1,2-dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

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11) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

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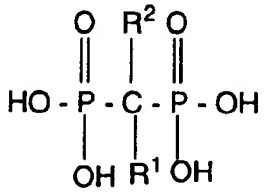
17. The pharmaceutical composition of Claim 10 wherein the bisphosphonate is alendronic acid, or pamidronic acid, or a pharmaceutically acceptable salt thereof, and
the growth hormone secretagogue is:
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;
or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of Claim 10 wherein the bisphosphonate is alendronic acid, or a pharmaceutically acceptable salt thereof, and the growth hormone secretagogue is:
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
or a pharmaceutically acceptable salt thereof.

19. A method for the treatment of osteoporosis which comprises administering to a patient in need of such treatment an effective amount of a combination of a bisphosphonate and a growth hormone secretagogue.

20. The method of Claim 19 wherein the bisphosphonate is of the formula:



X

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wherein:

R^1 is selected from the group consisting of:

(a) C_{1-5} alkyl, unsubstituted or substituted with:
  (1) NH_2,
  (2) pyridyl,
  (3) pyrrolidyl,
  (4) NR^3R^4
(b) NR^5,
(c) SR^6, and
(d) Cl;

R^2 is H, OH, or Cl;

R^3 is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-10} alkyl; and

R^6 is aryl;

or a pharmaceutically acceptable salt thereof.

21. The method of Claim 19 wherein the bisphosphonate is selected from alendronic acid, etidrononic acid, clodronic acid, pamidronic acid, tiludronic acid, risedronic acid, 6-amino-1-hydroxy-hexylidene-bisphosphonic acid, and 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid;

or a pharmaceutically acceptable salt thereof.

22. The method of Claim 21 wherein the bisphosphonate is alendronic acid or a pharmaceutically acceptable salt thereof.

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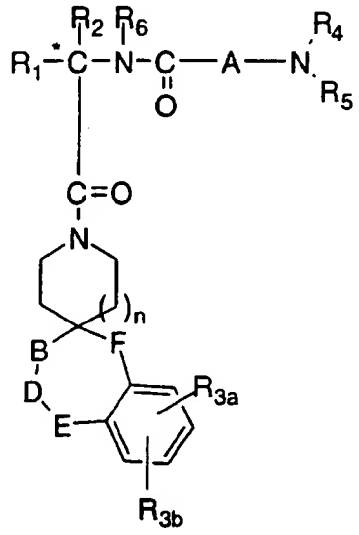
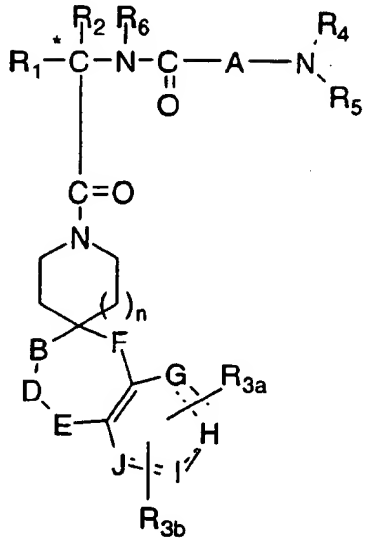
23. The method of Claim 19 wherein the growth hormone secretagogue is of the Formula I or II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl,

-aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, $OC(O)$, $C(O)O$, or $-CR_2=CR_2-$, or -C≡C-,

and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

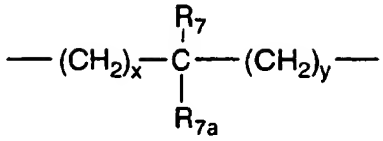
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

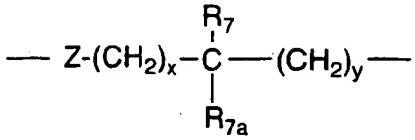
R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=0, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-C(O)OR_2, -(CH_2)$_q$-C(O)O(CH_2)$_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -C(O)OR_2;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -C(O)R_2, -C(O)(CH_2)$_q$-aryl, -SO_2R_2, -SO_2(CH_2)$_q$-aryl, -C(O)N(R_2)(R_2), -C(O)N(R_2)(CH_2)$_q$-aryl, -C(O)OR_2, 1-H-tetrazol-5-yl, -SO_3H, -SO_2NHC≡N, -SO_2N(R_2)aryl, -SO_2N(R_2)(R_2),
and wherein the (CH_2)$_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -O(CH_2)$_q$ aryl, 1 to 2 -C(O)OR_{2a}, 1 to 2 -C(O)O(CH_2)$_q$ aryl, 1 to 2 -C(O)N(R_{2a})(R_{2a}), 1 to 2 -C(O)N(R_{2a})(CH_2)$_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -C(O)NHSO_2R_{2a}, -S(O)$_m$$R_{2a}$, -C(O)N$HSO_2$($CH_2$)q-aryl, -$SO_2$NHC≡N, -$SO_2$NHC(O)$R_{2a}$, -$SO_2$NHC(O)($CH_2$)$_q$aryl, -N($R_2$)C(O)N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)N($R_{2a}$)($CH_2$)$_q$-aryl, -N($R_{2a}$)($R_{2a}$), -N($R_{2a}$)C(O)$R_{2a}$, -N($R_{2a}$)C(O)($CH_2$)q aryl, -OC(O)N($R_{2a}$)($R_{2a}$), -OC(O)N($R_{2a}$)($CH_2$)$_q$ aryl, -SO_2(CH_2)$_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

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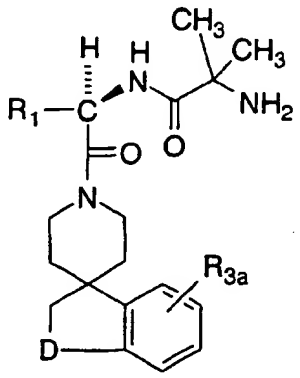
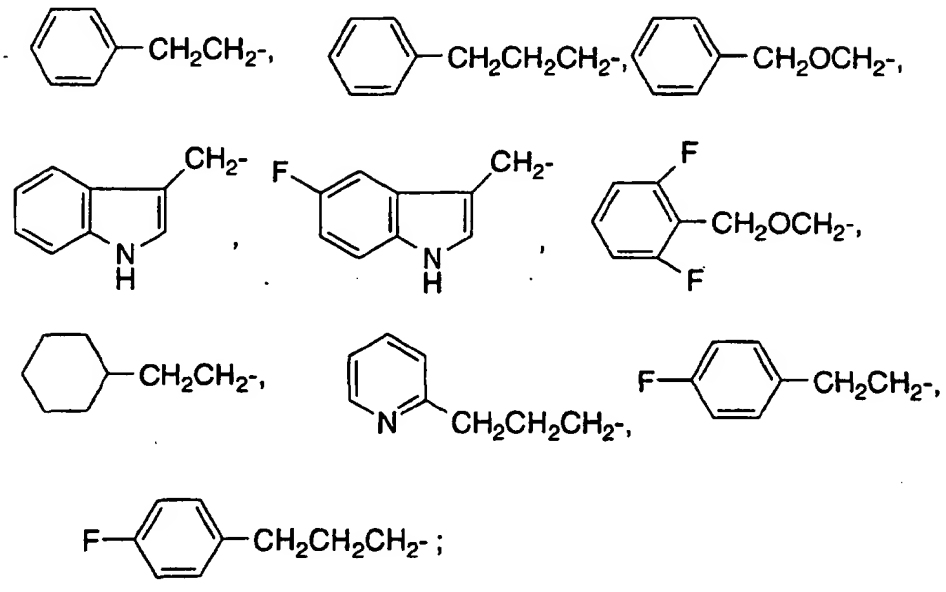
24. The method of Claim 19 wherein the growth hormone secretagogue is of the Formula V:



V

wherein:

R_1 is selected from the group consisting of:



R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)$_m$-, N(R2), $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $NSO_2(CH_2)_qC(O)$-$N(R_2)(R_2)$, N-$SO_2(CH_2)_qC(O)$-$N(R_2)(CH_2)_wOH$,

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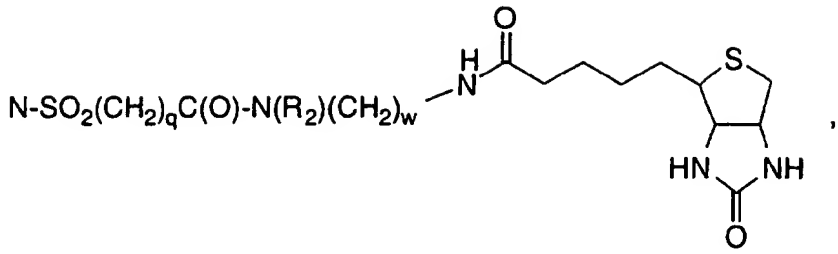

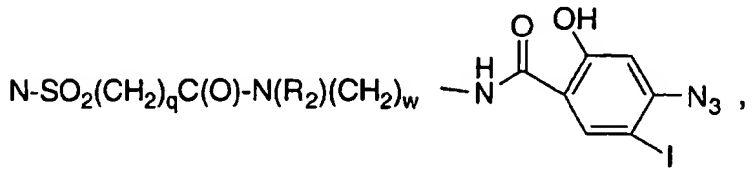

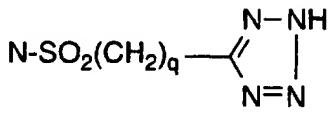

and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

25. The method of Claim 19 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

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2) N-[1(R)-[(1,2-dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

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26. The method of Claim 19 wherein the bisphosphate is administered at a dose of from 0.001 to 10 mg/kg of body weight and the growth hormone secretagogue is administered at from 0.0001 to 25 mg/kg of body weight.

27. The method of Claim 26 wherein the bisphosphonate is administered at from 0.01 to 1.0 mg/kg of body weight.

28. The method of Claim 19 wherein the bisphosphonate is alendronic acid, or pamidronic acid, or a pharmaceutically acceptable salt thereof, and
the growth hormone secretagogue is:
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;
or a pharmaceutically acceptable salt thereof.

29. The method of Claim 19 wherein the bisphosphonate is alendronic acid, or a pharmaceutically acceptable salt thereof, and the growth hormone secretagogue is:
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;
or a pharmaceutically acceptable salt thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11912

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/66, 31/445
US CL :514/ 108, 320
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 108, 320

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A, 94/13,696 (CHEN ET AL.) 23 JUNE 1994, SEE PAGE 3, LINE 5 TO PAGE 16, LINE 14 AND PAGE 50, LINES 15-33.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 DECEMBER 1994	Date of mailing of the international search report 09 JAN 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAYMOND J. HENLEY III Telephone No. (703) 308-1235

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